NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Inhaled corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over

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

Comment from	Comment	Response
GlaxoSmithKline (GSK)	Underpinning the recommendations made in sections 1.1 and 1.3 is the assumed clinical equivalence of ICSs at both the low and high doses. Indeed, the ACD concludes that there are few statistically significant differences between the ICSs (4.1.3) and that there was little evidence to reject the hypothesis that there is no difference in clinical effectiveness between them (4.1.4). However, these conclusions are inconsistent with the Appraisal Committee's summary (4.1.11) that there was "…little conclusive evidence of equivalence and more often there was inconclusive evidence concerning differential effectiveness." This suggests that the hypothesis of no difference should be rejected.	Comment noted – reword 4.1.11 The Committee concluded that overall there were no differences in the clinical effectiveness of the different ICS

Comment from	Comment	Response
GSK	Re 4.1.4 and 4.3.2 The assumption that fluticasone propionate (FP) is clinically equivalent even at half the daily dose of other ICSs is also inconsistent with systematic reviews undertaken by both the Cochrane Collaboration and by GSK. The Cochrane systematic review undertaken by Adams et al. concluded that at half the daily dose, fluticasone propionate (FP) produced a significantly greater improvement in lung function (both forced expiratory volume in one second (FEV_1) and morning peak expiratory flow (PEF)) compared with beclometasone dipropionate (BDP) or budesonide (BUD). Given that one of the main aims of asthma therapy is the achievement of best possible lung function, acknowledging the relative efficacy advantage of FP over BDP assists patient education and guides clinical choice of ICS.	Comment noted – no change Assessment Group response 'differences were observed for some measures (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. ' The BTS guidelines note the dose equivalence of ICSs compared to budesonide/beclometasone dipropionate and the experts were in agreement with this. The Committee concluded that on balance there is no evidence of a consistent difference in the effectiveness of the different ICS.

Comment from	Comment	Response
GSK	GSK would therefore urge that the clinical data is summarised consistently to reflect the above evidence, and in particular that FP is at least as clinically effective as BDP and BUD at half the daily dose, but may be superior in improving lung function. GSK therefore suggests that the wording for both of the recommendations made at 1.1 and 1.3 change from "…the least costly product that is suitable for the person is recommended." to "the least costly product taking into account the relative efficacy and safety is recommended".	Comment noted – no change No one ICS was better in terms of overall lung function –some RCTs showed improvements with various ICS in some but not all measures of lung function. The Assessment Group concluded and the Committee agreed that there were no consistent differences in the effectiveness of the various ICS. The clinical experts agreed with the Assessment Group's conclusions.
GSK	In previous comments to the Assessment Group GSK highlighted the inappropriate exclusion and inclusion of studies in the assessment of efficacy of Seretide™ (SFC) compared with an increased dose of ICS. On balance, however, the conclusions on clinical effectiveness in the ACD are reasonable in that the addition of a LABA in the form of a combination inhaler is statistically significantly superior to increasing the dose of ICS alone across a range of outcomes (see 4.1.5).	Comment noted. 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	The Appraisal Committee cite the cost effectiveness evidence arising from the Gaining Optimal Asthma control (GOAL) trial[6] but reference the Assessment Group's conclusion that the generalisability of this trial may be limited (4.2.1). However, there are no reasons to believe that GOAL is not generalisable to the UK. Indeed, the baseline demographics of the trial population are representative of asthma patients in the UK and thus are likely to achieve similar outcomes. In addition, the proportion of patients enrolled in the trial from the UK (n=294) exceeds an equal share given the number of countries (n=44) involved. Consequently, GSK suggests that the following sentence is added to the end of 4.2.1: "Despite this there is no reason to believe that GOAL is not relevant to the UK population".	Comment noted This was an economic evaluation. The reason the AG thought it not generalisable was not because of demographic factors but with regards to costs.
GSK	In addition to the GOAL economic analysis the recommendation in 1.2 is supported by cost effectiveness information provided by GSK, and recently published in a peer-reviewed journal, that shows that for patients uncontrolled on either BDP 400 or 800µg/day or equivalent, the cost per Quality Adjusted Life Years (QALYs) for SFC compared with increasing the doses of FP or BDP are below the £20,000 threshold.	Comment noted – no response required
GSK	Whilst GSK acknowledges the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guideline recommendation[10] of adding in a LABA rather than increasing the dose of ICS, GSK believes it would have been helpful to decision-makers if the Appraisal Committee had also highlighted that adding in a LABA is a cost effective approach.	Comment noted – no change. 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	The Assessment Group's comparison of costs that is referenced in 4.2.7 is based on only one of the two SFC devices, namely the Accuhaler®, which was used in the clinical trials reviewed. Given the clinical equivalence of the Accuhaler and Evohaler® 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.	Comment noted. The methodology of the TAR was to 'state what the annual cost of the preventer drugs would be using the equivalent products (in the UK) ***to those actually used*** in the trial' (TAR Pg 398)
GSK	The analysis reported in 4.2.7 also excluded two unpublished GSK trials (SAM30013 and SAM40120), which were the only trials relevant to this question that were conducted using the Evohaler device. The Assessment Group excluded these trials on the basis that they were not published and the study reports were not provided by GSK. However, GSK provided study reports for other studies as requested by the Assessment Group so it is not clear why the study reports for these two trials were not requested, although details of these studies were included in the GSK submission, listed in the data outline, and a summary available on the GSK clinical trial register website. As a result of this omission the cost-consequence analysis only reflects the cost of the Accuhaler device.	Comment noted – no change <u>Assessment Group response</u> "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 cost-consequence analysis alluded to in 4.2.7, SFC (Accuhaler) is cheaper than FP or BUD alone in two out of the five trial/cost comparisons, however, if the Evohaler device cost is used, the evidence would show that there is a cheaper SFC device in <u>all</u> trial comparisons.	Comment noted. See comments on methodology for the cost consequence analysis above.
GSK	GSK would request that it is made clear in this section that the cost differences are estimated using the Accuhaler device only, and that an additional sentence is included to state that "When the Evohaler device cost is included it is cheaper than either FP or BUD alone in all comparisons".	Comment noted – 4.2.7 has been reworded to clarify that the costs are based on the Accuhaler device

Comment from	Comment	Response
GSK	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.	Comment noted – no action required
GSK	Although the Appraisal Committee acknowledge the importance of adherence, GSK believes it would be helpful if the observational evidence base that supports this recommendation had also been reviewed and summarised in the guidance. This evidence was reviewed and summarised in GSK's submission (see section 3.10.5) and response to the Assessment Report (see page 2).	Comment noted – no change The outcome of adherence to ICS treatment was not included in the scope of the appraisal. The Committee were aware of the potential for improved adherence of taking ICS when combined with a LABA in a single inhaler (4.3.8).
GSK	Due to a misprint in the British National Formulary (March 2006), the incorrect cost for SFC was used in the Assessment Group's cost comparisons of SFC with ICS plus LABA in separate inhalers. After GSK highlighted this incorrect cost in comments on the Assessment Report, the Assessment Group revised the analysis. GSK requests that the Appraisal Committee's summary of the evidence includes this revised analysis. For example, in section 4.2.8, the last sentence "Only at a very high dose and using another device (Evohaler), the separate inhalers can be the cheaper option." is incorrect. As Table 2 [not reproduced here] shows, <u>both</u> SFC devices are always cheaper than it's components in separate inhalers at all doses.	Comment noted – costs have been updated in the FAD

Comment from	Comment	Response
GSK	Also in GSK's response to the Assessment Report and submission document, cost comparisons of SFC with BDP plus salmeterol in separate inhalers were provided, however, this evidence was not considered by the Assessment Group. As Table 3 [not reproduced here] shows, using a weighted average cost approach identical to that of the Assessment Group, SFC is cheaper than BDP plus salmeterol in all circumstances except at infrequently used high doses using the Evohaler device only. Given that salmeterol and BDP are used frequently together in separate inhalers in the NHS, GSK believes it would add value to also include information on these relative comparators.	Comment noted – no change The Committee considered the cost effectiveness of combination ICS + LABA inhalers compared with delivering the same products using separate inhalers. The Committee did not consider the use of a combination ICS/LABA compared with a different combination of ICS and LABA in different inhalers which would lead to different cost effectiveness estimates.
GSK	In addition, GSK has concerns about the conclusion in the guidance that "…there is no combination inhaler that is cheapest in all circumstances…" (4.2.9), and would suggest that this be reworded to "…with current costs there is always a cheaper Seretide device in all circumstances". This is consistent with the cost comparisons provided by both the Assessment Group and GSK, and reproduced in Table 4 [not reproduced here].	Comment noted – no change 4.2.9 clearly states that the fluticasone propionate/salmeterol Evohaler pMDI combination is cheapest at low and high doses.

Comment from	Comment	Response
GSK	GSK acknowledges the recommendation for pMDIs (1.4), as it is consistent with the recommendations within technology appraisal guidance no.38 and supported by the evidence assessed in the health technology assessment report for that appraisal. GSK suggests that inhalers should only be prescribed after a patient has received training in the use of the device and has demonstrated satisfactory technique in line with the BTS/SIGN guideline. If this can not be demonstrated the option of using a spacer could be considered. The use of a spacer should be reserved for patients who do not have the ability to use a pMDI on its own effectively. However, this treatment approach would not be necessary or suitable for all adult patients. Consequently, GSK suggests that the wording in section 1.4 be changed to "Whenever possible, taking into account sections 1.1 to 1.3, the use of press-and-breathe pressurised metered-dose inhaler (pMDI) is recommended in the first instance, **with use of a spacer if appropriate.** Thereafter, a therapeutically equivalent Dry Powder Inhaler (DPI) should be considered".	Comment noted – this part of the guidance has been deleted.
AstraZeneca	AstraZeneca is concerned that readers could misinterpret the recommendation in Section 1.2. AstraZeneca suggests the paragraph is amended to clarify the conclusions on the two combination inhalers. AstraZeneca suggest the paragraph is changed to: *1.2 For people in whom treatment with ICSs and long-acting beta-2 agonists (LABAs) is considered appropriate (step 3 of the BTS/SIGN guidelines), the use of a combination device is recommended as an option. The decision about whether to use a combination device or the two agents in separate devices should be made on an individual basis, taking into consideration the likelihood of treatment adherence as well as individual preferences. If both options are considered equally appropriate then the least costly product or combination of products that is suitable for the person is recommended, bearing in mind that no combination inhaler is cheapest in all circumstances.*	Comment noted – no change 1.2 has been rewritten as bullet points to clarify.

Comment from	Comment	Response
AstraZeneca	When the technology Assessment Report (TAR) was made available for consultation in January 2007, AstraZeneca commented that as well as comparing fixed dosing regimens of combination inhalers, the TAR should also include a discussion on the use of adjustable dosing which allows treatment to be tailored to individual patient's needs. AstraZeneca is surprised that the assessment groups have not supplied a response to this comment. In addition the ACD does not discuss the availability of flexible dosing with combination inhalers or the advantages they provide. For example, the combination inhaler Symbicort can be administered as Symbicort Adjustable Maintenance Dose (AMD) that maintains asthma control, while reducing exacerbations and drug load compared with fixed dosing. AstraZeneca received UK marketing authorisation for this in May 2001. AstraZeneca suggests that the Final Appraisal Determination (FAD) contains a discussion of the availability and benefit of adjustable dosing.	Comment noted – reword Text has been added to the FAD to indicate that Symbicort may be used in a flexible dosing regimen (3.1).

Comment from	Comment	Response
AstraZeneca	In Section 4.2.9 the conclusion is that there is no combination inhaler that is cheapest in all circumstances. AstraZeneca agrees with this, but would like to highlight three studies that were discussed in our submission of evidence. Firstly, a study of 1719 UK patients who were randomised to either budesonide/formoterol adjustable dosing or budesonide/formoterol fixed dosing demonstrated that adjustable dosing resulted in an annual per patient cost saving of £65.70. Secondly, in a randomised study of 1034 patients in Sweden, budesonide/formoterol adjustable dosing compared with budesonide/formoterol fixed dosing was associated with fewer exacerbations, fewer daily inhalations of budesonide/formoterol, and lower costs (six-month saving Euros 98, p<0.001). Finally, the reduction in exacerbations and reliever medication usage with budesonide/formoterol adjustable dosing compared to budesonide/formoterol fixed dosing was also demonstrated in a study of 658 patients. This reduction is also likely to lead to budesonide/formoterol adjustable dosing being associated with a lower cost than budesonide/formoterol fixed dosing. In light of these three studies and the potential of the paragraph being misinterpreted, AstraZeneca suggest that the paragraph be amended in the FAD to say: 4.2.9 *When comparing the costs of the two combination inhalers budesonide/formoterol and fluticasone propionate/salmeterol there is no combination inhaler that is cheapest in all circumstances, and the difference in cost of the cheapest options is minimal. For example, at the lower dose level the fixed dose 200mcg/6mcg budesonide/formoterol DPI taken one inhalation twice daily costs £231/year. The corresponding cost of fluticasone propionate/salmeterol will vary depending on the device that is prescribed. The fixed dose 100mcg/50mcg fluticasone propionate/salmeterol DPI taken one inhalation twice daily costs £379/year; whereas the fixed dose 50mcg/25mcg pMDI taken two inhalations twice daily costs £221/year. In addition, the use of adjustable dosing can reduce costs compared to fixed dosing.*	Comment noted – changes made to 4.2.9 but the costs of flexible dosing has not been included.

Comment from	Comment	Response
Teva (Ivax)	CFC-beclometasone Phase Out in the UK In October 2006, GSK advised the NHS that, in line with the requirements of the Montreal protocol under which the manufacture of CFCs is gradually being phased out, they would be discontinuing Becotide/Becloforte metered dose beclometasone inhalers during the second half of 2007. GSK currently supplies approximately 43% of the CFC-beclometasone metered dose inhalers (pMDIs) prescribed in the UK, and Teva UK Ltd, as the second largest supplier, cannot guarantee to supply beclometasone in a CFC pMDI for more than one year. Currently there are approximately 2 million patients that are receiving metered dose inhalers of CFC-beclometasone to control their asthma symptoms. In view of the above, the remaining preparations of CFC-beclometasone should not be included in any cost analysis or subsequent guidance as their supplies will be limited by the time the guidance is finalised. Conclusion The phase out of CFC containing beclometasone should be clearly communicated in the guidance as by the time it is published Becotide and Becloforte will no longer be available. The few remaining suppliers of CFC containing beclometasone, of which Teva UK Ltd is the largest, will have limited stocks remaining and this should be reflected in the guidance.	Comment noted – text added to FAD noting the withdrawal of CFC inhalers under the Montreal Protocol. See also 4.3.2 of the ACD and FAD.

Comment from	Comment	Response
Teva	CFC free Beclometasone – Guidance Summary Section 1 The current use of beclometasone in the UK accounts for around 77% of single inhaled corticosteroid usage (IMS March 2007). The BTS/SIGN guidelines currently recommend beclometasone based on its established safety and efficacy profile. As the mainstay of asthma management prescribers are likely to continue to prescribe beclometasone in a CFC free preparation. The guidance should therefore reflect the properties relating to the two CFC free beclometasone preparations and should clearly define the different potencies of the two products. Qvar being more potent than Clenil. The MHRA thought this important enough to issue recommendations in August 2006 to prescribe CFC-free beclometasone by brand Conclusion The different potencies of the two currently available CFC-free beclometasone products should be defined in the summary section of the NICE guidance.	Comment noted – text added to FAD as a preamble noting the withdrawal of CFC inhalers under the Montreal Protocol Section 4.3.2 notes that the QVAR HFA beclometasone propionate device delivers finer particles and is therefore more potent than other beclometasone dipropionate devices. The committee noted the information from the MHRA.

Comment from	Comment	Response
Teva	Breath Actuated Devices In the ACD section 3.2 there is some discussion of the use of breath actuated inhalers and it is stated that they cannot be used with spacer devices. This is incorrect as Beclazone Easi-Breathe (containing CFC-beclometasone) is only available in the UK in a pack that contains a dose optimiser (small volume spacer). The statement made in section 3.5 that breath actuated inhalers are more expensive than pMDI versions is incorrect. The breath actuated Qvar Autohaler is the same price as the Qvar pMDI version. The Qvar Easi-Breathe breath actuated device is less expensive than the pMDI. Conclusion Beclazone Easi-Breathe is supplied with a small volume spacer for use with the product. Although Qvar Autohaler and Qvar Easi-Breathe can be used with an aerochamber spacer device, they are rarely used together as no additional benefit in lung deposit is seen with a spacer.	Comment noted – rewording to FAD Text has been added to note that breath actuated inhalers are ***'in general'*** not used in conjunction with a spacer device and that ***'in general'*** breath-actuated MDIs are more expensive than those that are not breath actuated.
Teva	Cost Effectiveness of Qvar and Fluticasone Whilst this conclusion is supported in part in the Assessment Report by the comparison of CFC-free Inhaled Corticosteroid alternatives in the cost effectiveness section, we believe that several of the calculations are inaccurate and lead to false assumptions of the most appropriate treatment choice. The cost comparisons within the Assessment Report have been based on mean weighted and unweighted annual costs for each ICS. At the **lower starting dose of 400 µg/day**, excluding CFC-beclometasone products, **CFC-free beclometasone** was confirmed as the most cost effective option (most clinically effective at lowest cost. However, at the **higher 800 µg/day beclometasone equivalent dose, the Assessment Report showed fluticasone** to be the cheapest option. We have reviewed the data, based on the PCA 2005, and wish to make the following observations:	Comment noted – no change The Committee's recommendations that patients are treated with the least costly version of the most appropriate ICS which takes into consideration the different possible dosing regimens. Assumptions about how daily doses are assumed to be achieved (vis a vis strength of inhaler and puffs) is on Page 383 of TAR. The analysis also presents means that are weighted by usage.

Comment from	Comment	Response
Teva	**Fluticasone Low Dose**: Approximately 70% of fluticasone prescriptions are for the pMDI, in order to receive a 400 µg/day CFC-Beclometasone equivalent, the patient must take 4 doses of 50 µg of fluticasone (the cheapest fluticasone preparation) at an annual cost of £66.19. This is more expensive than Qvar at an annual cost of £62.82 for a 400 µg CFC-beclometasone equivalent dose. In addition, fluticasone 50 µg pMDI accounts for only 15% of all fluticasone prescriptions. **Fluticasone High Dose**: At a CFC-beclometasone equivalent of 1600 µg the only scenario there FP would be cheaper than Qvar would be if the patient were to take 16 doses of 50 µg. The weighted and unweighted means presented in the Assessment Report do not allow for the impracticality of this regimen, and since the most commonly prescribed fluticasone dose is 250 µg. It seems more likely that the patient would be prescribed 4 doses of the fluticasone 250 µg at an annual cost of £439.70, compared with £251.27 for Qvar 800 (1600 µg CFC-beclometasone equivalents).	FAD section 4.2.4 notes that weighted averages conceal wide variations in cost of individual preparations.
Teva	Conclusion We therefore contend that after the phase out of CFC containing beclometasone, CFC-free beclometasone will be the most cost effective ICS over the whole dose range. We believe that the cost comparisons should reflect commonly prescribed and practically used dosage regimens.	Preamble to the FAD notes the phase out of CFC inhalers

Comment from	Comment	Response
Teva	Use of Weighted averages Beclometasone is available in a number of different presentations, which have widely differing costs as recognised in the ACD. Currently 97% are prescribed as aerosol and 3% prescribed as the higher cost Dry Powder Inhalers. This use of weighted averages in the Assessment Report is misleading as it includes all devices without considering the differences in usages of the various devices. This assumption skews the analysis in favour of fluticasone, when CFC-beclometasone is clearly the more cost effective option. This is particularly evident when CFC beclometasone is removed as the current market share of DPI and HFA are applied to the whole market.- thus increasing the mean and median cost due to the higher price of the DPIs.	Comment noted – FAD section 4.2.4 notes that weighted averages conceal wide variations in cost of individual preparations.
Teva	We also question the calculation of the mean weighted and unweighted annual costs as these are based on the extent of beclometasone DPI prescribing after the CFC phase out. The calculation assumes that DPIs will represent 8% of the ICS usage rather than the current 3%, this is because the calculations relate to the quantities of DPI shown in the PCA 2005 are based on dose and not units prescribed. Conclusion We therefore conclude that Fluticasone is often not the lowest cost inhaled corticosteroid, and therefore the ACD conclusion is misleading.	The Committees recommendations that patients are treated with the least costly version of the most appropriate ICS which takes into consideration the different possible dosing regimens.
Royal College of nursing (RCN)	Section 1.4: MDI and spacer is often the first choice but we agree that not everyone can use them. A dried powder may be better.	Comment noted – no action required
RCN	Section 2.6: We consider that the last sentence needs more emphasis on the need for stepping down of treatment when necessary.	Comment noted – no change 4.3.5 notes the issues of people being on inappropriately high doses of ICS due to ‘stepping up’ during an exacerbation and not being ‘stepped down’.

Comment from	Comment	Response
RCN	Section 2.7: Data on the numbers of patients/percentages at each step would be useful.	Comment noted – no change This information was not submitted to nor considered by the Committee
RCN	Section 3.5: As CFCs containing products are being phased out, should we be advising that they are cheaper? The patient will only have to be changed off them.	Comment noted. Text on the phase out of CFC inhalers has been added to the preamble to the FAD
RCN	Section 4.3.5: We agree that stepping down would be useful.	Comment noted – no action required
RCN	In general, we welcome the patient choice and usability element of this health technology rather than the cheapest option. Clinician's choice is also important.	Comment noted – no action required
RCN	There does not seem to be any mention of having steroid warning cards at the higher doses of ICS. We suggest that this be added.	Comment noted – no change It is taken as read that any precautions specified in the SPC will be followed by prescribers and pharmacists dispensing the medication.
General Practice Airways Group (GPIAG)	**The title of the Appraisal ….** is still misleading and is at odds with the detail in the appraisal scope document. This is an appraisal of the "Comparative effectiveness and cost-effectiveness of Inhaled Corticosteroids for the treatment……." If this were a true appraisal of inhaled corticosteroids (ICS) then the long term side effects of ICS especially at high doses should be included, based on observational data. This is not an appraisal of oral corticosteroids, and the scope quite clearly includes only inhaled steroids. The title should be amended to reflect the scope of the appraisal as outlined in para 4.1.2.	Comment noted – Add 'inhaled' to the title

Comment from	Comment	Response
GPIAG	We welcome the recognition of the Appraisal Committee that the choice of delivery device is important when choosing an ICS, but are uncertain about the evidence behind the statement in 1.4 that "*use of a pressurised inhaler plus spacer is recommended in the first instance*." Whilst accepting that this is the first choice for delivery of inhaled corticosteroids in children and delivery of high doses in adults, we are not aware of evidence which supports the preferential use of spacers in adults with good inhaler technique, for the delivery of low dose inhaled steroids.	Comment noted – this guidance has been deleted from the FAD
GPIAG	There is not general agreement with the statement in para 4.3.6 that "*a pMDI (pressurised metered dose inhaler) and spacer device is usually considered in the first instance in routine clinical practice*". This is not the case in adults being prescribed low dose ICS where the pMDI alone is often the device of choice. Indeed there are disadvantages with the MDI-spacer approach: a. Extra cost to the NHS and to the patient of the spacer device. b. Use of a more cumbersome device for the patient.	Comment noted – see response above
GPIAG	In the absence of evidence that use of an MDI and Spacer is more effective or has less side effects for the delivery of low dose steroids in adults than the MDI alone, it would be more appropriate to say that "*Use of a pMDI is recommended in the first instance. Use of a spacer device is recommended for delivery of high dose inhaled steroids or for patients with poor inhaler technique*."	Comment noted – this has been deleted from the FAD.

Comment from	Comment	Response
GPIAG	Para 4.3.8 and para 4.3.9. 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 in 4.3.8 that "*separate devices in fully compliant individuals could be equally effective and equally or more cost effective*" and in para 4.3.9 that "*in the future delivery via separate inhalers in fully compliant individuals may become the preferred option*"	This sentence refers to the cost effectiveness of ICS + LABA in combination vs. separate devices, and reflects the possibility that although combination devices are currently the least costly option this could change in the future.
GPIAG	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.	Comment noted – no change The SPCs state that LABAs should be taken with a ICS for the treatment of asthma regardless of whether they are delivered in a single combination device or separate inhalers. The potential advantage of combination devices was noted by the committee.
GPIAG	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*".	Comment noted - see above response The SPCs state that LABAs should be taken with a ICS for the treatment of asthma regardless of whether they are delivered in a single combination device or separate inhalers.

Comment from	Comment	Response
GPIAG	Our final point is that there appears to be no section in the ACD for suggestions for 'Further research' as there is for most appraisals. We strongly recommend that the groups preparing the assessment report are asked for their views on the gaps in the research base for inhaled corticosteroids in asthma, and we have suggested the following research needs too - 1. Recognising the low adherence we see with ICS in practice and impact this has on asthma disease - what are the most cost-effective approaches to managing this? 2. More observational and real world studies in order that studies include the range of disease patterns that asthma manifests, and that the results of studies are generalisable to the heterogeneity of the patient population in primary care 3. The outcomes associated with a personal asthma action plan for patients in primary care (many studies are in secondary care) 4. Improving understanding of the unpredictable relationship between symptoms and measures of lung function 5. Longer term studies to explore the impact of treatment on long term control and exacerbations 6. Longer term studies to explore the impact of adherence on asthma outcomes related to different technologies	Comment noted – no change. These suggested recommendations refer to how to improve asthma management and are not limited to research on how to improve the delivery of ICS for chronic asthma (the remit of the appraisal).

Comment from	Comment	Response
DOH	We feel that there is an apparent lack of information regarding the effect of inhaled corticosteroids on growth in height of the over 12s, which may be particularly important at the time of normally accelerated pubertal growth. This is a key part of well being. The side effect on growth is touched on in the appraisal consultation document. (3.4), but does not appear to be discussed any further. It would be helpful to know whether there is any evidence (or lack of evidence) supporting the use of one inhaled steroid preparation over another, with respect to growth suppression.	Comment noted – text has been added to the FAD on adverse events associated with ICS.
Asthma and Allergy Research Group	Section 2.2: With regard to diagnosis of asthma,no mention is made wrt disconnect which is often found between airway calibre and the underlying inflammatory process ,and in particular airway hyperresponsiveness –ie patients may have normal values for FEV1 and PEF but have evidence of bronchoconstriction on challenge –eg with exercise ,allergen or non specific agents like histamine or methacholine or mannitol .	Comment noted
Asthma and Allergy Research Group	Section 3.5 : According to the BNF, breath actuated pMDI's are NOT more expensive than ordinary pMDI –eg comparing generic BDP as Beclazone pMDI to Beclazone Easibreathe, or comparing Qvar to Qvar Easibreathe or Autohaler .For this reason it makes sense to always prescribe a breath actuated pMDI for BDP as there is no cost difference .	Comment noted – text has been added to state that in general breath actuated pMDi are more expensive. The guidance only states the cheapest suitable product should be used. If price is equal then ease of use is important – pMDIs can be used with spacers and it is not clear that this is always the case with breath actuated devices.

Comment from	Comment	Response
Asthma and Allergy Research Group	Section 4.1.11 –I would refer to Gibson et al JACI 2007:119:344, which in an meta-analysis of 20 RCTs of 4312 patients showed no significant benefit on severe exacerbations [defined by need for oral steroids] by adding LABA to higher dose of ICS or to a similar dose in steroid naïve patients ,but only conferred significant benefit when LABA was added to same pre-existing dose of ICS [NNT =18] .The summary as stated is not supported by the data from meta-analysis wrt severe exacerbations for adding LABA to a higher dose of ICS	Comment noted – no change The paper is in agreement with the Assessment Group that asthma control was significantly improved when LABA was added compared to all ICS strategies. The TAR concluded that the ICS /LABA combination was significantly superior to increasing the dose of ICS across a range of outcomes and statistically superior to same dose ICS alone across most outcomes
Asthma and Allergy Research Group	4.3.5 The point has been missed here that for a given ICS the systemic adverse effects are dependent on the fine particle dose from the formulation – eg for FP there is a 5 fold difference in lung bioavailability when comparing FP via DPI vs FP via pMDI plus spacer [Wilson Lancet 1999;353:2128;Martin AJRCCM 2002;165: 1377].	Comment noted – 4.3.6. of the FAD has been reworded
	Also in 4.3.5 the point is missed that for FP the absorption from the lung is largely determined by airway calibre ,such that more severe patients are relatively protected from systemic adverse effects [Lee Ann Allergy Asthma Immunol 2004:93:253] –ie it is the unique interaction between the device and the patient that will be the major determinant of systemic effects –eg someone taking FP 2000ug via DPI with FEV1 of 50% will be very unlikely to develop systemic adverse effects ,but a patient taking FP 500ug via pMDI plus spacer with FEV1 of 90% will be at much greater risk	Comment noted
Clinical Expert	**Section 2.4, page 5** I would say mortality from asthma is unusual rather than rare. I think it is also worth making a point that numerous studies have shown that 90% of these asthma deaths are preventable.	Comment noted – 2.4. of the FAD has been reworded to include ‘unusual’

Comment from	Comment	Response
Clinical Expert	**Section 2.7, page 5** I think increasing the dose of inhaled steroids should be put before slow release beta 2 agonist tablets as slow release beta 2 agonist tablets tend to have quite a lot of side effects.	Comment noted – no change. This section reflects the recommendations of the BTS guidelines
Clinical Expert	**Section 2.7, page 6** The last sentence would better read 'The majority of people with asthma are treated at steps 1, 2 or 3.	Comment noted – FAD amended
Clinical Expert	**Section 2.8, page 6** I think it would be best to say that most exacerbations can be treated with high dose inhaled short acting beta 2 agonists and **often** a short course of oral steroids is needed.	Comment noted – FAD amended
Clinical Expert	**Section 3.1, page 6** The new combination inhaler of BDP and formoterol is now I think licensed and will shortly be marketed, should this be mentioned in this section?	Comment noted – the Institute was aware of the product but it could not be included in the appraisal having not received a marketing authorisation in the UK by the time the assessment report was circulated
Clinical Expert	**Section 3.4, page 7** I think the second part of this section needs to be put into context. I think it would be better to say 'In adults systemic adverse effects are very unusual in doses below 800 micrograms per day. Above this dose biochemical adrenocortical suppression may occur although it is extremely rare for this to be of clinical significance. A reduction in bone mineral density has been reported in some cross sectional studies but not others; any effect that is seen is small'. I'm sure Jonathan Gregg will comment on growth retardation in children but again I think this should be set into context by saying growth retardation has only been reported at above licensed doses.	Comment noted – section 3.4 of the FAD has been reworded

Comment from	Comment	Response
Clinical Expert	**Section 4.3.5, page 17** I think this should be reworded to say 'Clinical specialists noticed that higher doses of ICS (greater than 800 micrograms beclomethasone dipropionate equivalent) were associated with an increased risk of systemic adverse events. Although some small reductions in bone mineral density have been seen in some cross sectional studies it needs to be born in mind that high dose inhaled steroids are often used to prevent exacerbations which require courses of oral steroids which undoubtedly have deleterious effects on bone density'.	Comment noted – FAD has been reworded (4.3.6)
SHTAC and PenTAG	Paragraph 2.8. Sentence beginning 'Most exacerbations can be treated with high doses of inhaled SABAs'. We have amended our assessment report to make a distinction between mild and severe exacerbations as follows: "Minor exacerbations may be treated by the individual using high doses of inhaled SABAs or an increased dose of ICS, although sometimes a short course of systemic corticosteroids or other treatments are also needed.[1] More severe exacerbations, although less common, can potentially be life-threatening, and may require hospitalisation, treatment and monitoring until symptoms have stabilised". We suggest the ACD is amended accordingly.	Comment noted – FAD has been reworded as suggested
SHTAC and PenTAG	Section 4.1 Clinical effectiveness. Need to emphasise that the systematic review only included RCTs which compared inhaled corticosteroids using the same inhaler device in each trial arm. Suggest this goes at the end of 4.1.2	Comment noted FAD has been reworded as suggested
SHTAC and PenTAG	Paragraph 4.1.4. Sentence on dose ratios "For one comparison of HFA-beclometasone dipropionate the equivalent ratio to HFA-fluticasone propionate was assumed to be 1:1 rather than 1:2". This is the first time that dose ratios are mentioned in the ACD. Without any preceding information on the ratios that are generally accepted in clinical practice and by clinical guidelines this sentence doesn't really mean anything. Suggest adding in some text earlier on explaining about dose equivalence between the different ICS.	Comment noted FAD has been reworded as suggested

Comment from	Comment	Response
SHTAC and PenTAG	Paragraph 4.1.8 Suggest adding 'head to head' to first sentence: "Three RCTs compared the two available combination inhalers *head to head* in their dry powder form…."	Comment noted FAD has been reworded as suggested
SHTAC and PenTAG	Paragraph 4.1.11 Final part of final sentence is incorrect "…and that the two combination inhalers currently on the market were equally effective". As reported in the assessment report, results were mixed, with the fluticasone/salmeterol combination statistically superior on some outcomes, and the budesonide and formoterol combination statistically superior on other outcomes.	Comment noted FAD has been reworded as suggested

Comment from	Comment	Response
NHS Professional 1 (comment via web site)	I think 1.2 is in direct conflict with BTS recommendations. The whole purpose of which is to trial the use of LABA to determine if it does have benefit. If a clinician is given the option to go direct to a combination device IT WILL REMOVE a necessary step and potentially lead to increased cost for the NHS since we won"t be able to determine if it was the addition of the LABA or simply due to the fact the patient now also took the ICS which they might not have been taking appropriately before! If adopted this process will also force the use of fluticasone or Budesonide combination products after a patient has actually been treated previously on Beclometasone. The latter being the most cost effective ICS and if appropriate for the patient would be the one used (as proposed in 1.1 of these new guidelines). We would not have the choice to continue with Beclometasone IF a clinician wants to commence a ""combination"" device because one doesn"t exist for LABA + Beclometasone - again potentially increasing costs! (SECTION 1) We need the availability of a cost effective LABA/beclometasone combination device to allow continued treatment under the new proposals of allowing a combination device to be used IMMEDIATELY at step 3. (SECTION 3)	Comment noted – no change The BTS guidelines state that before proceeding to adding a LABA clinicians should check compliance and inhaler technique on ICS alone. The ACD assumes that at step 2 a trial of ICS and LABA will be conducted to assess the efficacy of the LABA. In patients who respond to ICS and LABA clinicians may chose to prescribe these products in a single combination device or separate inhalers. (1.2) Comment noted 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.
NHS Professional 2 (comment via web site)	From a practical point this may be an inconvenient device if the patient is on anything more than a B.D. regieme. (SECTION 1)	Comment noted – no change The method of administering ICS and LABA will depend on the individual patient's circumstances. (1.2)

Comment from	Comment	Response
NHS Professional 3 (comment via web site)	Not all patients like pMDI even though they are able to use them, which possibly affects compliance (SECTION 1)	Comment noted – this guidance has been deleted form the FAD
NHS Professional 4 (comment via web site)	1. Why mention slow release beta-2 agonist tablets, they are rarely used in clinical practice and of little benefit. 2. Re 2.8 - most exacerbations can be treated with increased SABAs, this is not in agreement with the basic principle of controlling airways inflammation and indeed can be dangerous. (SECTION 1) 3.4 - Has the link between ICS and osteoporosis been definitely proven? (SECTION 3.4)	Section 2 of the ACD describes the management of asthma as given in the BTS guidelines. Comment noted – FAD has been reworded to include more information on the adverse event profile of ICS
NHS Professional 5 (comment via web site)	In light of recent concerns about increased risk of severe asthma attacks in patients taking long-acting beta2-agonists, it is important to optimise inhaled corticosteroid treatment for the individual. Please stress to try 800mcg/day beclometasone equivalent (400mcg/day in children 12 and under) and give it sufficient time to work before moving to step 3. Promotion of combination inhalers is resulting in many patients potentially moving too early (and maybe unnecessarily) to step 3. Also emphasise that stepping down from step 3 to step 2 means stopping the LABA not reducing the ICS dose. (SECTION 1)	Comment noted – no change The BTS guidelines state that before proceeding to adding a LABA clinicians should check compliance and inhaler technique on 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
NHS Professional 6 (comment via web site)	1.1 In light of double potency of fluticasone, it seems prudent to recommend less potent agents at step 2 eg beclometasone or budesonide, reserving more potent agents for more severe disease (step 3 or 4). (Ref: MHRA. Current Problems in pharmacovigilance 2001:27:10) 1.2. It should be emphasised that the lowest effective dose of steroid is used at each step. Prescribers should be reminded of the importance of stepping down once control has been achieved. Note that some patients may be able to step down from step 3 to step 2 hence will require a combination preparation switching to a single steroid preparation. The use of combination inhalers cannot be advocated if patients are not regularly reviewed with a view to stepping down once control gained, as this will prolong the unnecessary use of LABAs. 1.4 The metered dose inhalers are not always the least costly product for ICS. The guideline should clarify the position of MDIs with respect to cost. 2.1 In the BTS/SIGN guidelines the peak flow recording is documented as the PEF (not PEFR) 4.1 ? what dose of Ciclesonide at step 4/5 is necessary. The SPC states that 160mcg daily is usually the maximum dose. Studies comparing ciclesonide to fluticasone suggested that much larger doses would be necessary to be used at the higher steps. The studies which evaluate dose comparisons to beclometasone are only available in abstract form to date. For these reasons it is difficult to advocate its use at the higher steps. 4.3.5 The reminder from the MHRA (Current Problems in pharmacovigilance 2001:27:10) recommends that doses of 500mcg bd of fluticasone are only prescribed for patients with severe asthma where benefit can be demonstrated by an improvement in lung function and or symptom control or ability to reduce oral steroid therapy. It suggests that the advice is specific to fluticasone and was updated to minimise the risk of systemic side effects with inhaled steroids. 4.3.6 The spacers are being recommended for preventer BD therapy and hence are not required to be portable. 4.3.8 ? evidence to support improved adherence. Only formoterol offers immediate bronchodilator effect. 4.3.8 Emphasise lowest effective dose - may need to change inhaler strength	Comment noted – no change Section 4.3.5 of the ACD notes concern that some patients are not stepped down at times of good control. 4.2.4 notes that in general MDIs are less expensive than DPIs, however it is difficult to be explicit about the cost of each device/drug preparation given the number of products. 2.1 Comment noted – PEFR changed to PEF 4.1 Comment noted. The use of ciclesonide is only recommended within the product license. 4.3.8 Evidence supporting improved adherence with a single combination inhaler (ICS + LABA) was provided by clinical specialists attending the meeting. Such comparisons 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.

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