

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

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

1 Guidance

The future discontinuation of CFC-containing inhalers will affect the range of devices available, but does not affect this guidance.

- 1.1 For adults and children aged 12 years and older with chronic asthma in whom treatment with an inhaled corticosteroid (ICS) is considered appropriate, the least costly product that is suitable for an individual, within its marketing authorisation, is recommended.
- 1.2 For adults and children aged 12 years and older with chronic asthma in whom treatment with an ICS and long-acting beta-2 agonist (LABA) is considered appropriate the following apply.
 - The use of a combination device within its marketing authorisation is recommended as an option
 - The decision to use a combination device or the two agents in separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence.
 - If a combination device is chosen then the least costly device that is suitable for the individual is recommended.

2 Clinical need and practice

- 2.1 Asthma is a chronic disorder of the airways, caused primarily by inflammatory processes and constriction of the smooth muscle in airway walls (bronchoconstriction). It is characterised by airflow obstruction and increased responsiveness of the airways to various stimuli. Symptoms include recurring episodes of wheezing, breathlessness, chest tightness and coughing. Typical asthma symptoms tend to be variable, intermittent and worse at night. Asthma is commonly triggered by viral respiratory infections, exercise, smoke, cold, and allergens such as pollen, mould, animal fur and the house dust mite.
- 2.2 It is estimated that there are 5.2 million people with asthma in the UK, of whom approximately 2.9 million are women and girls and 2.3 million are men and boys. This includes 0.7 million people older than 65 years and 0.6 million teenagers. The Health Survey for England (2001) estimated the lifetime prevalence of diagnosed asthma to be 16% in women and 13% in men. The 1998 figures from the General Practice Research Database, which sampled 211 general practices in England and Wales, estimated the age-standardised prevalence of treated asthma to be 7% in men and 8% in women. Mortality from asthma is rare (1266 asthma-related deaths were reported in 2004).
- 2.3 Asthma is diagnosed on the basis of symptoms and objective tests of lung function (such as peak expiratory flow rate [PEF] and forced expiratory volume in the first second [FEV₁]) and percentage predicted FEV₁ (calculated as a percentage of the predicted FEV₁ for a person of the same height, sex and age without diagnosed asthma). Variability of PEF and FEV₁, either spontaneously or in response to therapy, is a characteristic feature of asthma. The severity of asthma is usually judged according to the amount of medication required to manage the symptoms and is based on the BTS/SIGN guidelines.
- 2.4 Asthma usually develops in childhood but may start at any age. There is no cure for asthma, although people may experience long periods of remission.

Poorly controlled asthma can have a significant impact on the quality of life of the affected person and their family. However, there may be variation in an individual's perception of the symptoms and how he or she adapts to the condition over time. Clinical measures such as lung function may not correlate with an individual's quality of life scores, but if asthma is well controlled, near-maximal scores on quality of life instruments can be achieved.

- 2.5 Asthma management aims to control symptoms (including nocturnal symptoms and exercise-induced asthma), prevent exacerbations and achieve the best possible lung function, with minimal side effects of treatment. Current British guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) for the management of asthma recommend a stepwise approach to treatment in both adults and children¹. Treatment is started at the step most appropriate to the initial severity of the asthma, with the aim of achieving early control of symptoms and optimising respiratory function. Control is maintained by stepping up treatment as necessary and stepping down when control is good.
- 2.6 Mild intermittent asthma (step 1) is treated with inhaled short-acting beta-2 agonists (SABAs), as required. The introduction of regular preventer therapy with inhaled corticosteroids (ICSs; step 2) should be considered when a person has had exacerbations of asthma in the previous 2 years, is using inhaled SABAs three times a week or more, is symptomatic three times a week or more, or is waking at night once a week because of asthma. Add-on therapy (step 3) involves the introduction of an additional therapy, the first choice of which is an inhaled long-acting beta-2 agonist (LABA). Alternatives include orally administered leukotriene receptor antagonists, theophyllines and slow-release beta-2 agonist tablets, or increasing the dose of ICS. At step 4, further interventions may be considered if control remains inadequate on a

¹ The British Thoracic Society and Scottish Intercollegiate Guidelines Network (2003; updated 2005) British Guideline on the Management of Asthma: a national clinical guideline. SIGN Guideline No. 63. Edinburgh: Scottish Intercollegiate Guidelines Network. Available from <http://www.sign.ac.uk/guidelines/fulltext/63/index.html>

dose of ICS that is equivalent to 800 micrograms per day of beclometasone dipropionate in combination with a LABA, or following an unsuccessful trial of a LABA. Options include increasing the dose of the ICS to 2000 micrograms beclometasone dipropionate equivalent per day or adding a leukotriene antagonist, a theophylline or a slow-release beta-2 agonist tablet. At step 5, continuous or frequent courses of oral corticosteroids are introduced. The majority of people with asthma are treated at steps 1, 2 or 3.

- 2.7 Asthma exacerbations (or asthma attacks) are acute episodes of a progressive increase in shortness of breath, cough, wheezing or chest tightness, or a combination of symptoms. Exacerbations lead to the consumption of additional medications or to patient-initiated healthcare consultations, often in accident and emergency departments. Severe exacerbations can be life threatening. Minor exacerbations may be treated by the individual using high doses of inhaled SABAs although a short course of systemic corticosteroids is often also needed.

3 The technologies

- 3.1 ICSs suppress inflammation in the lungs and are recommended for prophylactic treatment of asthma. Five corticosteroids are available as inhaled formulations for the treatment of asthma: beclometasone dipropionate, budesonide, fluticasone propionate, mometasone furoate and ciclesonide. Two of the ICSs are available in combination with a LABA in a single inhaler (fluticasone propionate in combination with salmeterol and budesonide in combination with formoterol fumarate). The budesonide/formoterol fumarate combination device may be used as part of a flexible dosing regimen, such as adjustable maintenance dosing, and may also be used as a reliever medication.
- 3.2 The BTS/SIGN guidelines advise on equivalent doses of the different ICSs. Budesonide and beclometasone dipropionate are considered equivalent on a microgram for microgram basis (1:1 dose ratio). Half the dose of fluticasone

propionate, mometasone furoate or ciclesonide in micrograms is equivalent to a given dose of budesonide/beclometasone dipropionate (2:1 dose ratio). One type of hydrofluoroalkane (HFA)-propelled beclometasone dipropionate pMDI (QVAR) device delivers beclometasone dipropionate in extra fine particles so that more is deposited in the lungs, leading to a 2:1 dose ratio with the CFC budesonide/beclometasone dipropionate devices.

3.3 ICSs are available in a variety of devices. These are broadly of two types – pressurised metered-dose inhalers (pMDIs), in which the drug is suspended in either a chlorofluorocarbon (CFC) or HFA propellant, and dry powder inhalers (DPIs), in which there is no liquid propellant. It is expected that those using CFC propellants will soon be phased out in line with the Montreal Protocol. Many people have difficulty coordinating device actuation and inhalation with pMDIs. This can be overcome to some extent by using a spacer device to improve airway deposition and reduce oropharyngeal deposition, or by using ‘breath-actuated’ pMDI devices. DPIs deliver micronised drug, sometimes with a carrier powder, and use the individual’s own inspiratory flow to disperse the fine powder. Breath-actuated pMDIs and DPIs can be used to overcome the problem of actuation–inhalation coordination associated with pMDIs but DPIs and, in general, breath-actuated pMDIs cannot be used in conjunction with spacer devices.

3.4 Beclometasone dipropionate, budesonide and fluticasone propionate are available as pMDIs and DPIs. Ciclesonide is only available as a pMDI and mometasone furoate is only available as a DPI. The fluticasone propionate/salmeterol combination device is available both as a pMDI and as a DPI, and the budesonide/formoterol fumarate combination device is currently available as a DPI only. For further details of available products that are included in this appraisal please see appendix C.

3.5 The side effects of ICSs may be local (following deposition in the upper airways) or systemic (following absorption into the bloodstream). Local adverse effects include dysphonia, oropharyngeal candidiasis, cough, throat

irritation and reflex bronchospasm. Local adverse effects can be minimised by optimising inhaler technique and using a spacer with the inhaler device.

Systemic adverse effects include suppression of the hypothalamic-pituitary-adrenal axis, osteoporosis, skin thinning and easy bruising, cataract formation and glaucoma, and growth retardation in children and adolescents. Systemic adverse effects tend to be associated with higher doses of corticosteroids and can differ depending on both the drug and the delivery system. For full details of side effects and contraindications, see the summaries of product characteristics.

- 3.6 Each ICS is available in a variety of devices and strengths. In general, the DPIs are the most expensive and the CFC-containing products are the cheapest. Breath-actuated aerosol MDIs are generally more expensive than those that are not breath actuated. The CFC-free devices that contain a HFA propellant are more expensive than CFC-containing ones. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

- 4.1.1 There is a large body of evidence for the use of ICSs in asthma, with studies of various methodologies reported in the literature as well as unpublished studies submitted by manufacturers. The study populations are often hospital based and the inclusion and exclusion criteria frequently make them unrepresentative of the general population of people with asthma. The participants have varying severities of asthma and degrees of symptom control. The drugs are used in different doses, delivered by various devices, and they are compared with other drugs, devices, doses or placebo. The trials are generally of a short duration (up to 1 year). A variety of outcomes are

measured including changes in lung function such as FEV₁ and PEF, changes in asthma symptoms or the avoidance of exacerbations, and the use of short-acting bronchodilators or other medications. It is often unclear how these outcomes relate to quality of life.

4.1.2 The Assessment Group identified five questions relevant to this appraisal and conducted a systematic review in order to address them. The questions were as follows.

- Which ICS is the most clinically effective at low doses, equivalent to beclometasone dipropionate at a dosage of 200–800 micrograms per day (step 2 of the BTS/SIGN guidelines)?
- Which ICS is the most clinically effective at high doses, equivalent to beclometasone dipropionate at a dosage of 800–2000 micrograms per day (step 4 of the BTS/SIGN guidelines)?
- Which is the more clinically effective approach to introducing a LABA into a treatment regimen:
 - (a) increasing the dose of the ICS alone or adding a LABA to ICS treatment; or
 - (b) continuing with the ICS alone or adding a LABA to a similar dose of the ICS using a combination device (steps 2–3 of the BTS/SIGN guidelines)?
- Which is the more clinically effective treatment:
 - (a) fluticasone propionate/salmeterol in a combination device or the same drugs given in separate devices; or
 - (b) budesonide/formoterol fumarate in a combination device or the same drugs given in separate devices?
- Which is the more clinically effective treatment:

- (a) fluticasone propionate/salmeterol in a combination device or
- (b) budesonide/formoterol fumarate in a combination device (step 3 of the BTS/SIGN guidelines)?

- 4.1.3 The systematic review included only randomised controlled trials (RCTs) which compared ICSs using the same inhaler device in each trial arm. A total of 22 RCTs compared ICSs at low doses. All ICSs were compared with fluticasone propionate and budesonide but there were no pairwise comparisons between beclometasone dipropionate, mometasone furoate and ciclesonide. There were fewer studies for mometasone furoate and ciclesonide (three studies each) compared with the other drugs, which have been available for a longer period of time. The Assessment Group concluded that all the ICSs were associated with favourable changes from baseline to endpoint across efficacy outcomes. However, in pairwise comparisons, there were few statistically significant differences between the ICSs. The Assessment Group therefore concluded that it was reasonable to assume that there were no differences in clinical effectiveness between the different ICSs at low doses.
- 4.1.4 A total of 24 RCTs compared ICSs at high doses. Ciclesonide was compared only with fluticasone propionate; mometasone furoate was compared only with budesonide and fluticasone propionate. There were pairwise comparisons for all other drugs, with more evidence available for the older ICSs. For the comparison of one type of HFA-beclometasone dipropionate the equivalence ratio to HFA-fluticasone propionate was assumed to be 1:1 rather than 1:2. The Assessment Group concluded that all the ICSs were associated with favourable changes from baseline to endpoint across efficacy and safety outcomes. However, in pairwise comparisons, there were few statistically significant differences between the ICSs. The Assessment Group therefore concluded that it was also reasonable to assume that there were no differences in clinical effectiveness between the different ICSs at high doses.

- 4.1.5 Six RCTs compared combination devices containing a corticosteroid and a LABA with a device containing the same ICS alone at a higher dose. Four RCTs compared an ICS/LABA combination with a device containing a different ICS at a higher equivalent dose. Five studies compared the fluticasone propionate/salmeterol combination and five compared the budesonide/formoterol fumarate combination with a higher equivalent dose of ICS alone. There were no comparisons of the combination devices with beclometasone dipropionate, mometasone furoate or ciclesonide alone. Only trials in which the LABA and ICS were delivered in a single combination device were considered. The Assessment Group found that generally the addition of a LABA was statistically significantly superior to increasing the dose of ICS across a range of outcomes related to lung function, symptoms, rescue medication use and, to a lesser extent, asthma exacerbations.
- 4.1.6 Nine RCTs compared a combination device of an ICS and a LABA to the same dose of ICS alone. Six of these compared the fluticasone propionate/salmeterol combination with fluticasone propionate alone, and the remaining three were comparisons of the budesonide/formoterol fumarate combination with budesonide alone. The dose of ICS used in the studies varied. There were statistically significant improvements in lung function, asthma symptoms and rescue medication use favouring the combination treatment. The benefit in terms of frequency of exacerbation was not so marked, and there were no significant differences in adverse effects.
- 4.1.7 Six RCTs compared an ICS and LABA in a combination device with the two drugs delivered via separate devices. The two available combination devices (fluticasone propionate/salmeterol and budesonide/formoterol fumarate) were compared with their component drugs (three and two studies, respectively). One study compared the fluticasone propionate/salmeterol combination device with budesonide and formoterol fumarate as individual components. No comparisons were made with any other ICS/LABA combination. Because many of these studies used a double-blind double-dummy design (the patients taking a combination device also received a placebo dummy) these

studies would not be expected to fully capture any benefits of improved treatment adherence with a combination device. There were very few statistically significant differences between the treatments across various efficacy outcomes, and for some outcomes (for example, lung function) non-inferiority was demonstrated. Meta-analysis revealed no statistically significant differences in adverse events.

4.1.8 Three RCTs compared the two available combination devices head to head in their dry powder form (DPIs) and all were in the low-to-medium range of the ICS dose. The outcomes in terms of lung function, asthma symptoms and exacerbations were mixed. Meta-analysis found no statistically significant differences in rates of adverse events.

4.1.9 Seven submissions were received from manufacturers. Four of these concentrated on the delivery device, which was either a DPI with improved characteristics or contained a non-CFC propellant with improved delivery properties. One submission concentrated on an ICS alone and two concentrated on the LABA/ICS combination in a single device. In general, the submissions focused on each manufacturer's products only and no systematic comparison of all available products was made.

4.1.10 In summary, the Assessment Group concluded that, when comparing the different ICSs, either at low or high doses, there was no difference between them in terms of effectiveness. It also concluded that adding a LABA is more effective than continuing on the same or an increased dose of ICS. When considering simultaneous treatment with a LABA and an ICS, the Assessment Group concluded that it was reasonable to assume that there was no significant difference in effectiveness when these were administered in a combination device as opposed to separate devices. The Assessment Group also concluded that comparisons of the two combination devices showed mixed results, with the fluticasone/salmeterol combination being statistically superior for some outcomes and the budesonide/formoterol combination being statistically superior for other outcomes.

4.2 *Cost effectiveness*

- 4.2.1 The Assessment Group conducted a systematic review of published economic evaluations of asthma and identified 15 studies. Four studies were analysed from the UK NHS perspective but only one calculated an incremental cost per quality-adjusted life year (QALY). This analysis produced incremental cost-effectiveness ratios (ICERs) of £4800 to £18,300 per QALY gained for fluticasone propionate/salmeterol compared with fluticasone propionate alone at various dose levels. However, the analysis pooled effectiveness and resource-use data from patients in 44 countries and, for this reason, the Assessment Group concluded that the generalisability of these results to the UK setting may be limited.
- 4.2.2 Seven submissions were produced by six manufacturers (Altana, AstraZeneca, GlaxoSmithKline, IVAX, Meda and Trinity Cheisi). There was no submission from the manufacturer of mometasone furoate (Schering-Plough). All manufacturers produced a cost-minimisation analysis for the ICS products but none of the submissions compared all five available ICSs. Four submissions focused on either the device or the propellant associated with the ICS and one on the ICS itself. Two submissions produced a cost-effectiveness analysis for the combination devices from a product-specific perspective.
- 4.2.3 The Assessment Group addressed the economic evaluation of the five questions addressed in the effectiveness section (see section 4.1.2). Two of the questions relate to the comparison of ICSs as monotherapy at low and high doses, while three address the use of combination therapy (adding a LABA to ICS treatment compared with increasing the dose of ICS; treatment with separate devices compared with a combination device; and comparing the available combination devices). Where consistent evidence of differential clinical effectiveness was lacking, a cost-minimisation approach was used. If there was relatively consistent evidence showing differential effectiveness, a cost-consequence approach was adopted.

4.2.4 To generate a single cost figure for each ICS, a mean annual per-patient cost was calculated. This mean was presented as the average (unweighted) cost of a particular ICS, or the average cost weighted by usage based on the 2005 market share of different ICS preparations. As any particular target daily dosage can be achieved in a number of ways given the multiplicity of inhaler strengths available on the market, it was assumed that a dosage would be achieved in a fixed manner using higher strength inhalers to achieve higher total dosages. The BTS/SIGN guideline assumptions on the equivalence of doses of different ICSs were applied (see section 3.2). In addition to the mean annual per-patient cost being calculated for all currently available products, it was also calculated with CFC-containing products excluded, because it is expected that these will soon be phased out. Because there are a limited number of combination device products, the mean cost was calculated for each product. In general, the DPIs are more expensive than other device types. The cheapest products are pMDIs that contain CFCs and, with their withdrawal, the overall cost of ICSs will increase. The average costs conceal a wide variation in the cost of individual preparations for each drug. While the most expensive devices for any ICS have similar costs there is a wide variation in cost among the cheapest available devices.

4.2.5 At the lower end of the low-dose range (400 micrograms beclometasone dipropionate equivalent per day), the cheapest ICS is beclometasone dipropionate with an average cost of £65 per year. When CFC-containing products are excluded the cost increases, but beclometasone dipropionate remains the cheapest ICS (average cost of £79 per year). Excluding CFC-containing products has no effect on the mean costs of fluticasone propionate, mometasone furoate or ciclesonide because these are available only as CFC-free products. At the upper end of the low-dose range (800 micrograms beclometasone dipropionate equivalent per day), beclometasone dipropionate is the cheapest product with an average cost of £130 per year. When CFC-containing products are excluded, fluticasone propionate becomes the cheapest option if a weighted mean is considered.

- 4.2.6 In the high-dose range (800–2000 micrograms beclometasone dipropionate equivalent per day), only four ICSs were compared because ciclesonide is not licensed for use at an equivalent dose. The cheapest option is beclometasone dipropionate with an average cost of £198 per year. When CFC-containing products are excluded, fluticasone propionate is the cheapest ICS because cheaper CFC-containing beclometasone dipropionate products currently occupy a larger market share.
- 4.2.7 A cost-consequence analysis was conducted because the review of clinical effectiveness found that the ICS/LABA combination therapy was more effective than ICS monotherapy using an increased dose of ICS. The cost consequence comparison for the fluticasone propionate/salmeterol combination device was based solely on the device used in the relevant clinical trials (Accuhaler device) and not the least costly available device. At the low end of the dose range of ICS, the annual cost of the fluticasone propionate/salmeterol device is £92 more than fluticasone propionate alone at a higher dose. However, at the higher end of the dose range, the cost of the fluticasone propionate/salmeterol combination is £35 less than the ICS alone at a higher dose. When comparing the fluticasone propionate/salmeterol combination with budesonide alone at a higher dose, the combination treatment ranges from £94 cheaper to £109 more expensive depending on the budesonide preparation chosen. The budesonide/formoterol fumarate combination varies from being £163 cheaper to £66 more expensive than a higher dose of either fluticasone propionate or budesonide alone. No comparisons were made between the combination devices and other ICSs as monotherapy. The cost-consequence analysis above omits any potential cost savings that may result from avoidance of exacerbations as well as any potential quality-of-life gains associated with better asthma symptom control.
- 4.2.8 When the cost of taking a combination device is compared with taking the components separately, the combination product is almost always cheaper than taking the same drugs in separate devices. For the budesonide/formoterol fumarate combination, annual savings vary from £36

to £227 depending on the daily dose of ICS and the preparation of the LABA used. For the fluticasone propionate/salmeterol combination the annual savings vary from £39 to £185.

- 4.2.9 At the lower dose level (400 micrograms budesonide and 200 micrograms fluticasone propionate), the cheapest combination device is the fluticasone propionate/salmeterol aerosol pMDI, which costs £219 per year and is only £12 cheaper than the budesonide/formoterol fumarate DPI. The annual cost of low dose fluticasone propionate/salmeterol delivered by DPI (£379) is £148 more costly than budesonide/formoterol fumarate DPI (£231). At the higher dose level (800 micrograms budesonide and 500 micrograms fluticasone propionate), the fluticasone propionate/salmeterol DPI and pMDI are the cheapest at £446 per year, which is £16 cheaper than the budesonide/formoterol fumarate DPI.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ICSs, having considered evidence on the nature of the condition and the value placed on the benefits of ICSs by people with asthma, those who represent them, and clinical specialists. The Committee also considered the existing NICE technology appraisal guidance 38. The Committee was also mindful of the BTS/SIGN guidelines on the management of asthma, and of the need to take into account the effective use of NHS resources.
- 4.3.2 The Committee considered the evidence on the clinical effectiveness of ICSs and their use within the context of the BTS/SIGN guidelines on the management of asthma. Clinical specialists were in agreement with the dose-equivalence estimates for the effectiveness of CFC preparations of ICS, as presented in the BTS guidelines, but noted that the evidence base for determining the dose equivalence of mometasone furoate and ciclesonide relative to other ICSs was smaller. The specialists also stated that the Qvar

brand of HFA-beclometasone dipropionate delivers smaller particles of ICS, which leads to improved lung deposition. Therefore, it may be given at lower doses than beclometasone dipropionate delivered using a CFC propellant to achieve an equivalent effect. The Committee was also aware that CFC devices will be phased out in the near future in accordance with the Montreal Protocol.

- 4.3.3 The Committee understood the importance of using an ICS in the context of a pathway of care that includes informing people about their condition, involving them in their asthma management using a personal action plan, training them in the effective use of the delivery device, and regular review of the effectiveness of their treatment.
- 4.3.4 The Committee considered the different types of inhaler devices in children aged 5 to 15 years of age in line with technology appraisal guidance 38. The Committee considered that this guidance remains appropriate, being based on an assessment of good-quality evidence regarding the effective deposition of ICSs in the lower respiratory tract. The specialists agreed that this guidance for young asthmatics also applies to the use of ICSs in adults and that, for ICSs, a pMDI and spacer device is usually considered in the first instance in routine clinical practice, especially when high doses of ICS are required and where patients have difficulty using a pMDI correctly. The Committee heard from experts that spacers may not always be appropriate for adults, particularly when using low-dose pMDIs because local deposition and systemic absorption were likely to be good without a spacer. Patient experts also stated that some people do not use spacer devices because they consider them to be cumbersome. The Committee accepted the approach recommended in technology appraisal 38 and concluded that although pMDI and a spacer where appropriate should be considered in the first instance, where there is evidence that a person is not able to use a pMDI and spacer effectively, or if this approach is not appropriate for the agent chosen, then alternative devices should be considered.

- 4.3.5 The Committee first considered the RCT evidence on the clinical effectiveness of ICSs at doses equivalent to beclometasone dipropionate up to 800 micrograms per day. The Committee heard from clinical specialists that the RCTs recruited a selected group of individuals with better compliance with treatment and inhaler technique than is generally seen in clinical practice. The Committee heard from the specialists that, although there is little evidence of statistically significant differences in the clinical effectiveness of ICSs from the RCTs, in clinical practice some people respond to some agents/inhaler device systems better than others. They stated that at low doses of inhaled steroids (below the beclometasone dipropionate equivalent of 800 micrograms), few people experience local or systemic adverse effects. However, they added that in a small minority of people who experience local side effects (even at low doses) the use of pro-drugs, which are converted to an active form only once they reach the lungs (for example, ciclesonide), may be of use. The specialists agreed that, at low doses, there was a low risk of systemic adverse effects with ICSs. The Committee concluded that there is little difference in the clinical effectiveness of different products when delivered appropriately at low doses.
- 4.3.6 The Committee considered the RCT evidence on the clinical effectiveness of higher dose ICSs (doses equivalent to greater than 800 micrograms beclometasone dipropionate). Clinical specialists noted that higher doses of ICSs were associated with an increased risk of systemic adverse events, although the extent of this risk was poorly quantified and based on observational studies with conflicting results. The Committee considered the possible effect of ICSs on growth in adolescents. The Committee heard from clinical specialists that in clinical practice, other factors such as choosing the most appropriate device were considered to be more important than the impact on growth, and therefore this was not seen to be an overriding factor in considering which product to use. The specialists agreed that people's treatment should be initiated and maintained on the lowest possible dose of ICS that controls their symptoms. They expressed concern that some people

may be on inappropriately high doses of ICSs because treatment has been 'stepped up' during an exacerbation but not 'stepped down' when good control of asthma was achieved. The Committee was aware that an individual's propensity for experiencing side effects at high doses of ICS was dependent on the pharmacokinetics of the ICS as well as the physical properties of the delivery system and other factors that determine lung deposition such as airway calibre. Based on the evidence from RCTs, the Committee concluded that at equivalent doses there is little difference in the effectiveness or adverse-event profile of the different ICSs and also concluded that treatment with the lowest effective dose of ICS was most appropriate.

- 4.3.7 Two clinical specialists and one patient expert attended the Appraisal Committee meeting. They agreed with the conclusion of the assessment report that there are no consistent differences between the clinical effectiveness of the different ICSs or the different ICS/LABA combinations. They also emphasised the need for choice to individualise patients' treatment with a wide range of delivery devices. They provided insight into the importance of the type of device to adherence and overall clinical effectiveness of asthma treatment.
- 4.3.8 The Committee considered evidence on the relative cost effectiveness of the different ICS products for the treatment of asthma. The Committee was aware of the variation in the price of different manufacturer's products of the same ICS and the variation in price of the different types of inhaler devices. The Committee concluded that, in light of the assumed equivalence of the clinical effectiveness of the different ICS products, the least costly product that can be used effectively by an individual should be chosen.
- 4.3.9 The Committee considered the RCT evidence on the addition of a LABA to ICS treatment in people who are not adequately controlled on an ICS alone at step 3 of the BTS/SIGN guidelines. The Committee noted from the evidence that the addition of a LABA to the current dose of ICS is more clinically

effective than increasing the dose of ICS (in the absence of a LABA). The Committee were in agreement with the BTS/SIGN guidelines on the introduction of LABA to people not adequately controlled on ICS alone (step 3) and therefore did not consider it necessary to make a separate recommendation concerning when a LABA should be added to ICS treatment. The Committee was also aware that LABAs are licensed only for use in people with asthma who are already taking an ICS. It also noted that there were no consistent differences between the two combination devices currently available in terms of clinical effectiveness.

4.3.10 The Committee considered that treatment with an ICS plus a LABA in a single combination device was at least as effective as using the same ingredients in separate devices. The Committee heard from clinical specialists and patient experts that the use of a single combination device is associated with significantly improved adherence. The Committee was aware that clinicians should take into consideration the individual's therapeutic need, including their ability to adjust the ICS dose in relation to the LABA, which is one of the benefits of using separate devices. However, the Committee was also aware of the safety issues arising from prescribing two separate devices (for example, preferential use of the LABA and omission of ICSs) and that the budesonide/formoterol combination device could be used in flexible dosing regimens. In conclusion, the Committee was persuaded that decisions should be made on an individual patient basis taking into account the therapeutic need, and that the use of a single combination device would normally be preferred to the use of two separate devices. However, the Committee agreed that there might be circumstances when separate devices in fully compliant individuals could be equally clinically effective and equally or more cost effective.

4.3.11 The Committee considered the evidence on the cost effectiveness of ICSs plus LABA treatment using a single combination device or separate devices. The Committee noted that the use of a combination device (ICS plus LABA) can be cost saving compared with using separate devices. The Committee

also considered that, in people for whom ICS plus LABA treatment is appropriate, the least costly delivery method should be used, which is currently a combination device. The Committee was aware that future changes in the availability and relative cost of generic ICSs, LABAs and combination products (ICS plus LABA in a single device) may alter the relative cost effectiveness of delivery using a combination device compared with separate devices so that, in the future, delivery via separate devices in fully compliant individuals may become the preferred option. However, based on the current availability and relative pricing of combination devices, the Committee was persuaded that, at present, combination devices would be preferable. The Committee also noted that using a single combination device decreased the prescription cost for the individual.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS

Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX).

[Note: tools will be available when the final guidance is issued]

6 Related NICE guidance

- Inhaler devices for routine treatment of chronic asthma in older children (aged 5–15 years). NICE technology appraisal guidance 38 (2002). Available from: www.nice.org.uk/TA038
- Inhaler systems (devices) in children under the age of 5 years with chronic asthma. NICE technology appraisal guidance 10 (2000). Available from: www.nice.org.uk/TA010

NICE is developing the following guidance (details available from www.nice.org.uk).

- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years (publication expected November 2007)
- Omalizumab for severe persistent allergic asthma (publication date to be confirmed).

7 Review of guidance

- 7.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 7.2 The guidance on this technology is considered for review in November 2012. A five year review date is proposed as it is not expected that further research will substantially change the recommendations of this appraisal.

David Barnett
Chair, Appraisal Committee
June 2007

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with the chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam

Radiologist, St George's Hospital, London

Professor AE Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Anne Allison

Nurse Clinical Adviser, Healthcare Commission

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice,
University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital,
Blackpool

Professor Christopher Eccleston

Director Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical Ltd

Ms Linda Hands

Clinical Reader in Surgery, University of Oxford

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Terry John

General Practitioner, The Firs, London

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Dr Simon Maxwell

Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queens Medical Research Institute, University of Edinburgh

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Ann Richardson

Lay Member

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Simon Thomas

Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust

Mr David Thomson

Lay Member

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, School of Medicine, Cardiff University, Cardiff

Dr Paul Watson

Director of Commissioning, East of England Strategic Health Authority

B. NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Eleanor Donegan and Elangovan Gajraj

Technical Leads

Janet Robertson

Technical Adviser

Alana Miller

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG), Peninsula Medical School and Southampton Health Technology Assessments Centre (SHTAC), Wessex Institute for Health Research and Development (WIHRD), University of Southampton.

- Shepherd J, Rogers G, Anderson R et al. ICS and LABAs for the treatment of chronic asthma in adults and children aged 12 years and over: Systematic review and economic analysis, December 2006

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination:

I Manufacturer/sponsors:

- Altana Pharma Ltd
- AstraZeneca UK Ltd
- GlaxoSmithKline UK Ltd
- IVAX Pharmaceuticals UK Ltd
- Meda Pharmaceuticals Ltd
- Ranbaxy UK Limited
- Schering-Plough Ltd
- Trinity-Chiesi Pharmaceuticals Ltd

II Professional/specialist and patient/carer groups:

- Action Against Allergy
- Allergy UK

- Asthma UK
- British Lung Foundation
- British Paediatric Respiratory Society
- British Thoracic Society
- Cochrane Airways group
- Department of Health
- Education for Health
- General Practice Airways Group
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Physicians of Edinburgh
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Asthma and Allergy Research Group, University of Dundee
- AstraZeneca UK Ltd
- British National Formulary
- GlaxoSmithKline UK Ltd
- IVAX Pharmaceuticals UK Ltd
- Meda Pharmaceuticals Ltd
- Medicines and Healthcare products Regulatory Agency
- Merck Pharmaceuticals Ltd
- Napp Pharmaceuticals Ltd
- National Coordinating Centre for Health Technology Appraisal
- NHS Quality Improvement Scotland
- Peninsula Technology Assessment Group
- Ranbaxy UK Limited
- Respiratory Research Group, University of Glasgow
- Southampton Health Technology Assessment Centre, University of Southampton

- TEVA UK Ltd
- Trinity-Chiesi Pharmaceuticals Ltd

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on inhaled corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD:

- Professor Neil Barnes, Consultant Respiratory Physician nominated by British Thoracic Society – clinical specialist
- Dr Jonathan Grigg, Professor of Paediatric and Respiratory Medicine nominated by Royal College of Paediatrics and Child Health – clinical specialist
- Mrs Jennifer Versnel, Executive Director, Research & Policy nominated by Asthma UK – patient expert
- Dr Mike Thomas, External Affairs Liaison nominated by General Practice Airways Group – clinical specialist

Appendix C. Products included in appraisal.

Beclometasone dipropionate is available in MDIs with CFC-propellants and in breath activated MDIs in both proprietary (Becloforte, Allen and Hanburys; Becotide, Allen and Hanburys) and non-proprietary formulations (AeroBec, 3M; AeroBec Forte, 3M; Beclazone Easi-Breathe, IVAX; Filair, 3M; Filair Forte, 3M; Pulvinal BDP, Trinity). It is also available as an MDI with non-CFC propellants (Qvar, IVAX), DPIs (Asmabec Clickhaler, Celltech; Becodisks, Allen and Hanburys; Easyhaler, Ranbaxy) and hard capsule powder inhalers (BDP Cyclocaps, APS).

Budesonide is available in MDIs with CFC-propellants in both proprietary (Pulmicort, AstraZeneca) and non-proprietary formulations (Novolizer, Meda), DPIs (Pulmicort Turbohaler, AstraZeneca) and hard capsule powder inhalers (BUD Cyclocaps, APS).

Fluticasone propionate is available in MDIs with non-CFC propellants (Flixotide Evohaler, Allen and Hanburys) and in DPIs (Flixotide Accuhaler, Flixotide Diskhaler Allen and Hanburys).

Ciclesonide is available in MDIs with non-CFC propellants (Alvesco, Altana).

Mometasone furoate is available in DPIs (Asmanex Twisthaler, Schering-Plough).