NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

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

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the Assessment Report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Asthma is a chronic inflammatory disorder which leads to narrowing of the airways. This is caused primarily by inflammatory processes and constriction of the smooth muscle in airway walls (bronchoconstriction). Symptoms include recurring episodes of wheezing, breathlessness, chest tightness and coughing. Asthma symptoms tend to be variable, intermittent and worse at night.

Asthma is commonly triggered by viral respiratory infections and allergens such as pollen, mould, animal fur, house dust mites, cold and exercise.

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.

Asthma is diagnosed on the basis of symptoms and objective tests of lung function (such as peak expiratory flow rate [PEFR] and forced expiratory volume in the first second ([FEV1]). The normal between subject variation in maximally achievable FEV1 is reflected in reference values used to calculate lung function as a percentage of that predicted for a person of similar height, sex, age and race (weight is also sometimes considered) without a diagnosis of asthma (FEV1 % predicted). The severity of asthma is usually judged according to the amount of medication required to manage the symptoms and is based on the British Thoracic Society (BTS) guidelines (see section 1.2 for further details).

The Health Survey for England (2001) interviewed 15,647 adults aged 16 years or older and estimated the lifetime prevalence of diagnosed asthma to be 13% in men and 16% in women. Approximately 1% of these men and women had been diagnosed within 12 months of the survey. 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 7.3% in men and 7.65% in women.

Mortality from asthma is rare with 1,266 asthma-related deaths reported in 2004 (70% were in people over the age of 65). Audits of asthma deaths have identified several risk factors for asthma mortality, including disease severity, interaction with healthcare professionals before and during the fatal episode, health behaviour (such as reduced compliance with prescribed medication, poor inhaler technique and reduced contact with primary care services) and adverse psychosocial factors.

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 their symptoms (regardless of clinical status) and how they adapt to their condition over time. Clinical measures such as lung function may not correlate with an individual's quality of life, but if asthma is well controlled, near-maximal scores on quality of life instruments can be achieved.

1.2 Current management

The aim of asthma management is to control the symptoms, prevent exacerbations and achieve the best possible lung function, with minimal side effects. A variety of strategies are used in the management of the condition. Pharmacological management includes drugs such as inhaled corticosteroids (ICSs), and short- and long-acting beta2 agonists (SABAs/LABAs). The majority of people can control their asthma with regular ICSs supplemented by occasional doses of inhaled SABAs. However, some patients will need additional medication such as an inhaled LABA.

Current British guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment.[1] Treatment is started at the most appropriate step with the aim of achieving early control of symptoms and optimisation of peak flow rates. Treatment can be stepped up as necessary and stepped down when control is good.

Step one (mild intermittent asthma) is treated with inhaled SABAs as required. Patients move into **step two** (regular preventer therapy) when they have had exacerbations of asthma in the last 2 years, are using inhaled SABAs three times a week or more, are symptomatic three times a week or more, or are waking at night because of asthma once a week. In step two, ICSs are introduced. **Step three** involves the introduction of an additional therapy, the first choice of which is an inhaled LABA. Alternatives include

[1] British Guideline on the Management of Asthma: a national clinical guideline. The British Thoracic Society and Scottish Intercollegiate Guidelines Network. SIGN Guideline No. 63 Revised November 2005 available from URL http://www.sign.ac.uk/guidelines/fulltext/63/index.html

orally administered leukotriene receptor antagonists, theophyllines and slow-release beta2-agonist tablets. In **step four**, further interventions may be considered if control remains inadequate on a dose of ICS which is equivalent to 800 micrograms of beclometasone dipropionate in combination with a LABA (or following an unsuccessful trial of a LABA). Options include increasing the dose of ICS to 2000 micrograms per day, adding a leukotriene antagonist, a theophylline or a slow-release beta2 agonist. In **step five** continuous or frequent courses of oral corticosteroids are introduced. The majority of people with asthma are treated at steps one and two, although consultees have indicated that prescribing is not always in accordance with these guidelines.

A large proportion of individuals with asthma are managed in primary care, often within nurse-led clinics. General practitioners are encouraged to perform annual reviews on all registered asthma patients which includes an assessment of symptoms, exacerbations and lung function. However, many patients are reluctant or unable to attend these reviews. Clinical experts noted the importance of involving the patient in managing their asthma through education and by using a personal action plan.

Asthma exacerbations (or asthma attacks) are acute events which lead to the consumption of additional medications or to patient-initiated healthcare consultations, often in expensive healthcare settings such as A&E.

Several types of inhaler device have been developed in order to deliver drugs directly to the airways. Metered dose inhalers (pMDIs) are pressurised inhalers, some of which are breath activated. The drug is formulated either as a suspension in a carrier liquid or as a solution which is delivered through a chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellant. Studies of some HFA-propelled pMDIs have shown that the HFA propellants deliver fine particles resulting in a greater proportion of the drug being deposited in the small airways, compared with a similar CFC pMDI. Use of a spacer device in conjunction with a pMDI can also alter patterns of lung deposition and increase the total proportion of the drug delivered to the lower airways. Dry

powder inhalers (DPIs) are easier for patients to use correctly, however, lung deposition is flow-dependent and requires a forceful, deep inhalation.

Inhaler technique, individual preference and cost are all factors that may guide healthcare professionals in their choice of inhaler device. This appraisal focuses on a comparison of drugs rather than devices. NICE has issued guidance on inhaler devices for routine treatment of chronic asthma in younger children (aged under 5 years; NICE technology appraisal guidance 10) and older children (aged 5-15 years; NICE technology appraisal guidance 38).

Two important components of asthma management are patient compliance with medication and optimising inhaler technique. Consultee submissions noted that patients often take medication in response to symptoms with a 'stop-start' pattern of ICS use. A Cochrane review found that patients took the recommended dose of ICS medication on 20-73% of days and estimated average compliance with the prescribed dose of ICS to be between 63% and 92%. Records from the General Practice Research Database found that over a 10-year period only 42% of individuals obtained a repeat prescription for inhaled corticosteroids within the expected timeframe of the preceding prescription.

Correct use of an inhaler is essential if the anticipated dose is to be delivered successfully to the correct area within the lungs. Poor inhaler technique is most common with 'press and breathe' pMDIs as a result of poor coordination between the actuation of the aerosol and the correct inhalation effort. Studies in adults have shown that physician-assessed inhaler technique is "good" in between 5% and 86% of participants. Consultee submissions from clinical experts suggest that the ease of use of the inhaler device and the effectiveness of lung deposition of the ICS may explain improved compliance with dry powder inhalers and breath-actuated inhalers over pMDIs. Using an inhaler that combines an ICS and LABA may result in better adherence to treatment because patients perceive the immediate benefits of the LABA. Consultees noted that non-adherence to ICS therapy is a significant problem

and recommendations should take into account the complex needs of individuals and the importance of patient preference with the overall aim of improving correct usage of ICS treatment.

Common local adverse events related to ICSs are dysphonia, oropharyngeal candidiasis, cough, throat irritation and reflex bronchoconstriction. These adverse events may be mitigated by the use of a spacer with the pMDI. Common systemic adverse events that are potentially associated with long term ICS use include adrenal suppression, growth retardation in infants, children and adolescents, skin thinning and easy bruising, cataract formation and glaucoma. One of the major concerns of long-term ICS use is the potential for adverse effects on bone turnover (reduced bone formation and increased bone resorption), which can result in osteoporosis and fracture.

Consultees highlighted the variation in response to different pharmacological treatments.

2 The technologies

ICSs suppress inflammation in the lungs and are therefore the mainstay in the prophylactic treatment of chronic asthma. Regular treatment with an ICS reduces inflammation, swelling and mucus production in the lungs, resulting in better airflow in and out of the airways. ICSs also lead to fewer exacerbations, better control of symptoms and improved lung function, ultimately leading to a reduction in hospital admissions and deaths from asthma.

Five ICSs are available as licensed preparations for 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. Seretide (fluticasone propionate/salmeterol) is available both as a pMDI and as a DPI, while Symbicort (budesonide/formoterol fumarate) is currently available as a DPI only.

Beclometasone dipropionate, budesonide, and fluticasone propionate are available as pMDIs and DPIs. Ciclesonide is available as a pMDI only, while mometasone furoate is available as a DPI only. Pressurised metered dose inhalers can be given via a spacer to improve airway deposition and reduce oropharyngeal deposition. Budesonide and fluticasone propionate are also available in formulations for nebulisation.

A table describing the technologies (non-proprietary and proprietary name, dose and cost) is given in appendix B.

3 The evidence

3.1 Clinical effectiveness

The manufacturers' submissions in general provide evidence to support their own products. The studies cover a wide range of doses, different severities of asthma as well as variable degrees of control of asthma. Studies also vary in their duration as well as the comparator used.

3.1.1 GSK – Flixotide and Seretide

The manufacturer conducted a systematic review of the literature to assess the efficacy and safety profile of Flixotide (fluticasone propionate) and Seretide (fluticasone propionate/salmeterol). Only head-to-head comparisons of drugs were considered. Fluticasone propionate was compared to beclometasone dipropionate, which was assumed to be dose equivalent to budesonide. The manufacturer concluded that fluticasone propionate was as effective as beclometasone dipropionate in achieving a wide variety of outcomes at half the dose. The submission also concluded that while the adverse event profiles of fluticasone propionate and beclometasone dipropionate were generally similar, some studies showed that fluticasone propionate had less effect on bone mineral density and hypothalamus-pituitary-adrenal axis suppression than beclometasone dipropionate.

A total of 14 studies compared Seretide (fluticasone propionate/salmeterol combined inhaler) to the same dose of beclometasone dipropionate or fluticasone propionate and a further six studies compared Seretide with an increased dose of budesonide or fluticasone propionate. A meta-analysis showed an improvement in terms of lung function, symptoms and quality of life for Seretide. Six studies showed equivalent efficacy between Seretide and its components (fluticasone propionate/salmeterol) in separate inhalers. However, the double-blind, double-dummy design of these studies would not capture the possible advantages of improved compliance with a single combined inhaler, as suggested in observational studies.

Seretide was also compared to Symbicort (budesonide/formoterol fumarate). In equivalent doses and with similar management strategies they have equivalent outcomes in terms of lung function and asthma control. However, these conclusion are based on two studies.

3.1.2 AstraZeneca – Pulmicort and Symbicort

The submission discusses the pharmacokinetics of Pulmicort (budesonide) DPI and presents studies of the effectiveness of budesonide across a range of doses.

Budesonide is assumed to be equivalent to beclometasone dipropionate on a microgram-for-microgram basis. The Pulmicort DPI requires lower doses of budesonide to maintain asthma control than beclometasone dipropionate delivered via pMDI or Diskhaler. One study suggested microgram-for-microgram equivalence with fluticasone propionate delivered by a DPI. It is noted that a Cochrane review suggests that fluticasone propionate is equivalent to budesonide at a 1:2 dose ratio.

Three studies are described comparing Symbicort with its components (budesonide/formoterol fumarate) delivered via separate inhalers. No studies found any significant differences in terms of symptoms, lung function, rescue medication use or exacerbations. However, one study found fewer withdrawals from treatment in the Symbicort group, which the manufacturer interpreted as improved compliance. Two studies were identified that compared Symbicort with Seretide (fluticasone propionate/salmeterol). Used

in fixed doses and at equivalent (equipotent) doses of the ICS, there were no significant differences between Symbicort and Seretide in terms of the primary outcomes.

The submission also discusses further treatment strategies with Symbicort. These are the adjustable maintenance dosage (AMD) and Symbicort as maintenance and reliever therapy (SMART). In addition a systematic review and meta-analysis was performed to compare Symbicort (fixed dose combination) to various alternative maintenance therapies including: ICS alone (budesonide), Symbicort AMD, and salmeterol/fluticasone in a single inhaler.

3.1.3 Altana – Alvesco

The submission describes the effectiveness over a wide range of Alvesco (ciclesonide) doses in all severities of asthma from a series of unpublished papers. The manufacturer concludes that ciclesonide given once daily is comparable, at a 1:1 dose ratio, to fluticasone propionate administered twice daily via a DPI or hydrofluoroalkane-propelled pMDI and that it is equivalent to budesonide and beclometasone dipropionate at a 1:2 dose ratio. Ciclesonide is equally effective whether given morning or evening. In addition, the studies suggest that the adverse event profile of ciclesonide is comparable to that observed with placebo in the trials.

3.1.4 Ivax – Qvar

The submission emphasises the need to phase out CFCs. The smaller particle size delivered using Qvar (hydrofluoroalkane-propelled beclometasone dipropionate pMDI) results in a higher proportion of the drug being deposited in the lungs. Qvar is also available in a breath-actuated device which aids patient coordination. Qvar is considered equivalent to fluticasone propionate in a 1:1 dose ratio and to current preparations of beclometasone dipropionate and budesonide in a 1:2 dose ratio. The submission discusses four Cochrane reviews of the effectiveness of beclometasone dipropionate and other studies of the comparative efficacy of

beclometasone dipropionate through Qvar or other devices and other ICSs (fluticasone propionate/budesonide).

3.1.5 Meda – Novolizer

When compared with Pulmicort Turbohaler DPI, Novolizer (budesonide delivered by DPI) achieves a finer particle size and better lung deposition that is less dependent on the user's lung function.

When compared with Pulmicort Turbohaler DPI in a randomised trial, budesonide delivered via the Novolizer was found to be as efficacious for outcome measures of lung function and symptom control. One post-marketing surveillance study of patients showed improvements in asthma control with budesonide delivered via the Novolizer. The manufacturer concludes that this demonstrates the benefits of the device in real-life settings.

3.1.6 Trinity Chiesi – Pulvinal and Clenil Modulite

Pulvinal (a beclometasone dipropionate DPI) is a high resistance device which achieves good lung deposition even at low flow rates. The manufacturer concludes that Pulvinal has been shown to be as efficacious as other beclometasone dipropionate containing preparations as well as Pulmicort (budesonide).

The Clenil Modulite (hydrofluoroalkane-propelled beclometasone dipropionate pMDI) is designed to optimise particle size to facilitate the switch from current CFC-containing beclometasone dipropionate inhalers without the necessity for changing the dose (as with Qvar). Clenil Modulite is equivalent to CFC-containing beclometasone dipropionate inhalers over a range of doses in asthma of varying severity according to study data reported in confidence by the manufacturers.

3.1.7 Evidence from the Assessment Group systematic review

The Assessment Group identified a total of 84 studies which were relevant to the appraisal; 67 randomised controlled trials (RCTs), seven systematic reviews and 10 conference abstracts. These studies varied widely in terms of patient characteristics, duration, regimens, outcomes and methodological

quality. There were more studies of the more established ICSs (beclometasone dipropionate, budesonide and fluticasone propionate) and fewer of the newer ICSs (mometasone furoate and ciclesonide). The most commonly reported outcomes were lung function, symptoms, use of rescue medication and adverse events. However, no standard measures were used consistently in trials. For example, FEV1 was expressed as either an absolute change or as a percentage of the predicted FEV1. Inconsistencies in the way that symptoms and exacerbations were reported prevented clear comparisons and pooling of the data. Lung function is thought to be the most objective measure of response to treatment as it is likely to closely reflect the underlying disease process.

The effectiveness of ICSs and LABAs have been reported within the context of the BTS/SIGN guidelines to address the following five issues:

- to identify the most effective ICS at low doses (step 2)
- to identify the most effective ICS at high doses (step 4)
- whether an ICS alone or combination with LABA is more effective at step 2-3 of the guidelines
- whether combination treatment with ICS and LABA is more effective in a single or separate inhaler (step 3)
- to identify whether the Seretide (fluticasone propionate/salmeterol) or Symbicort (budesonide/formoterol fumarate) combination inhaler is most effective at step 3 of the guidelines.

The BTS/SIGN guidelines advise on equivalent doses of the different ICSs. Budesonide and beclometasone dipropionate have a 1:1 dose ratio in most devices, whereas half the dose of fluticasone propionate, mometasone furoate or ciclesonide is equivalent to a given dose of budesonide/beclometasone dipropionate (that is, 2:1 budesonide/beclometasone diproprionate: fluticasone propionate/mometasone furoate/ciclesonide). The hydrofluoroalkane-propelled beclometasone dipropionate pMDI inhaler 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 inhalers.

3.1.7.1 Comparisons of inhaled corticosteroids at low doses

A total of 22 RCTs evaluated the effectiveness of low-dose ICS using pair-wise comparisons. All of the ICSs were associated with favourable changes from baseline for safety and efficacy outcomes, and pair-wise comparisons demonstrated few differences between ICSs.

Five RCTs, which compared beclometasone dipropionate with budesonide (1:1 dose ratio), showed no significant differences in most outcome measures, although lung function (FEV1) favoured budesonide in two of the RCTs.

Five of the six RCTS comparing fluticasone propionate with beclometasone dipropionate (1:2 dose ratio) showed no statistically significant differences. One RCT reported a statistically significant improvement with fluticasone propionate for outcomes of lung function (morning PEFR), symptoms and the use of rescue medication.

Five RCTs comparing fluticasone propionate with budesonide (four at a 1:2 dose, and one at a 1:1 dose) reported mixed results. On measures of lung function, no significant differences were reported in any of the studies. Two RCTs, both using a 1:2 dose ratio, reported a significantly greater improvement in symptom scores with fluticasone propionate. Meta-analysis of three out of the four 1:2 dose ratio studies reported a significantly lower rate of adverse events with budesonide.

One RCT of ciclesonide vs budesonide reported no significant differences, and non-inferiority of ciclesonide compared to budesonide was demonstrated for the primary outcome measure of lung function (FEV1 and PEFR).

Two RCTs of mometasone furoate compared with budesonide (one at a 2:1 dose ratio and one at 1:1, 1:2 and 1:4 dose ratios) reported statistically significant differences in favour of mometasone furoate for lung function (FEV1 and PEFR), symptoms and the use of rescue medication at a 1:1 dose

ratio. The studies also found statistically significant differences in favour of mometasone furoate at a 1:2 dose ratio for lung function (FEV1) and asthma symptoms.

Two RCTs of ciclesonide and fluticasone propionate (1:1 and 1:2 dose ratios) reported no statistically significant differences and non-inferiority of ciclesonide at equivalent doses, and statistically significant improvements in fluticasone propionate for lung function (PEFR) at a 1:2 dose ratio.

One RCT of mometasone furoate and fluticasone propionate showed no statistically significant differences at a 1:1 dose ratio, but a statistically significant improvement in favour of fluticasone propionate for lung function (morning PEFR) and nocturnal waking at a 1:2 dose ratio.

3.1.7.2 Comparisons of inhaled corticosteroids at high doses

A total of 24 RCTs evaluated the effectiveness of high-dose ICS as pair-wise comparisons. All of the ICSs were associated with favourable changes from baseline for safety and efficacy outcomes, and pair-wise comparisons demonstrated few differences between ICSs.

Two RCTs of beclometasone dipropionate and budesonide (1:1 dose ratio) demonstrated no differences between the ICSs, except in the use of rescue medication which was significantly lower with budesonide.

A total of 10 RCTs compared fluticasone propionate with beclometasone dipropionate (two at 1:1 and eight at 1:2 dose ratios). The two trials that compared 1:1 doses reported mixed results. One reported a statistically significant improvement in lung function (FEV1 and PEFR) and a statistically significant reduction in exacerbations with fluticasone propionate compared to beclometasone dipropionate. The other RCT showed no statistically significant differences between the drugs.

One RCT reported no significant differences between hydrofluoroalkane-propelled beclometasone dipropionate and hydrofluoroalkane-propelled fluticasone propionate (1:1 dose ratio).

One of the six RCTs that evaluated the effectiveness of fluticasone propionate against budesonide (three at 1:1 and three at 1:2 dose ratios) reported significant improvements in lung function (FEV1 and morning PEFR) with fluticasone propionate.

One RCT of mometasone furoate and budesonide (1:2 dose ratio) reported statistically significant improvements in lung function (FEV1) with mometasone furoate.

Three RCTs of ciclesonide and fluticasone propionate (1:1 dose ratio) reported non-inferiority of ciclesonide for lung function.

One RCT of mometasone furoate and fluticasone propionate (1:2 dose ratio) reported no significant differences.

3.1.7.3 Evaluation of adding LABA to inhaled corticosteroid therapy

3.1.7.3.1 ICS compared to ICS plus a LABA (ICS at the same dose in both treatment arms)

Nine RCTs compared adding a LABA to ICS treatment using a combination inhaler with ICS alone (using the same dose of ICS as in the combination inhaler). Six studies compared Seretide (fluticasone propionate/salmeterol) with fluticasone propionate, and three compared Symbicort (budesonide/formoterol fumarate) with budesonide.

The six RCTs of Seretide vs fluticasone propionate varied in ICS-dose from 200 to 1000 micrograms per day. Seretide was associated with improved outcomes for lung function, which reached statistical significance in two of four studies measuring FEV1 and in all three studies which measured PEFR. Seretide also improved asthma symptoms (reaching statistical significance in three of five studies), and reduced the use of rescue medication in all studies. There was no difference in the rate of adverse events between these treatment regimens.

Three RCTs evaluated Symbicort (budesonide/formoterol fumarate) vs budesonide. The ICS dose varied from 200 to 1000 micrograms per day. All trials reported a statistically significant improvement with the combination inhaler for most outcomes (PEFR, FEV1, symptoms, and the use of rescue medication). One RCT reported a statistically significant improvement in nocturnal waking with the combination inhaler. None of the RCTs reported a significant difference in the rate of exacerbations or adverse events with Symbicort compared with budesonide alone.

3.1.7.3.2 ICS compared to ICS plus a LABA

A total of 10 RCTs compared adding a LABA to ICS treatment using a combination inhaler with ICS alone (a lower dose of ICS was used in the combination inhaler).

Five RCTs compared Seretide (fluticasone propionate/salmeterol) with ICS (fluticasone propionate was used as the comparator in two RCTs, budesonide was used in three RCTs). In general, combination treatment was statistically superior to increasing the dose of ICS across a range of outcomes.

Five RCTs compared Symbicort (budesonide/formoterol fumarate) with ICS (budesonide was used as the comparator in four RCTs, fluticasone propionate was used in one RCT). The combination inhaler was associated with statistically significant improvements in lung function (PEFR and FEV1) and the use of rescue medication, but not symptoms, compared with fluticasone propionate alone. Overall the combination inhaler was superior to budesonide alone for most efficacy outcomes. One RCT of Symbicort compared with budesonide (in which adjustable maintenance dosing [AMD] was introduced after 4 weeks in the Symbicort arm) reported no difference in the rate of exacerbations between the treatment regimens when budesonide/terbutaline was used as rescue medication, but reported a statistically significant reduction in the rate of exacerbations with AMD budesonide/formoterol fumarate when the combination inhaler was used as rescue medication (compared to budesonide and terbutaline).

3.1.7.4 Comparison of ICS plus LABA delivery using a combination vs separate inhalers

Six RCTs evaluated combination treatment using a single combination inhaler compared with separate inhalers; one RCT of Seretide (fluticasone propionate/salmeterol-combination) vs budesonide/formoterol fumarate (separately), three RCTs of Seretide vs fluticasone propionate/salmeterol (separately), and two RCTs of Symbicort (budesonide/formoterol fumarate - combination) vs budesonide/formoterol fumarate (separately).

One RCT compared Seretide (fluticasone propionate 500 micrograms per day/salmeterol 100 micrograms per day) vs budesonide (1600 micrograms per day) and formoterol fumarate (24 micrograms per day) in separate inhalers using a DPI in both treatment groups. The aim of this study was to demonstrate equivalence of the combination inhaler with the separate inhaler regimen. Lower doses of fluticasone propionate in the Seretide combination were shown to have similar efficacy to a higher dose of budesonide plus formoterol fumarate taken using separate inhalers. Rates of exacerbations were lower with Seretide but there were more adverse events (91 with Seretide compared with 78 for budesonide plus formoterol fumarate – statistical significance was not reported).

Three RCTs compared the delivery of fluticasone propionate/salmeterol (with 200-1000 micrograms fluticasone propionate and 100 micrograms salmeterol in each arm) in a single inhaler compared to separate inhalers using DPI devices in both treatment groups. Efficacy outcomes with the combination inhaler were shown to be equivalent to the separate inhalers and there were no significant differences between treatments.

Two RCTs compared the delivery of Symbicort (budesonide/formoterol fumarate) (with 640-800 micrograms budesonide and 18 micrograms per day formoterol fumarate) in a single inhaler compared to the separate ingredients using dry powder inhaler devices in both treatment groups. No statistically significant differences were found in terms of lung function, symptoms, quality of life or the rate of adverse events.

3.1.7.5 ICS/LABA delivery using Seretide (fluticasone propionate/salmeterol) compared with Symbicort (budesonide/formoterol fumarate)combination inhalers

Three RCTs evaluated the effectiveness of Symbicort (budesonide/formoterol fumarate) (approximately 800 micrograms budesonide, 24 micrograms formoterol fumarate using the Turbohaler DPI device) with Seretide (fluticasone propionate/salmeterol) (approximately 500 micrograms fluticasone propionate, 100 micrograms salmeterol using the Diskus [Accuhaler] DPI device). Results of these studies were mixed. Some studies reported statistically significant improvements for some outcomes with Symbicort (budesonide/formoterol fumarate) while others reported statistically significant improvements with Seratide.

One RCT reported significant improvements in lung function with the Symbicort inhaler, and two RCTs reported significant improvements in lung function with the Seretide inhaler. Two RCTs reported a significant reduction in the rate of exacerbations with the Symbicort inhaler, and one RCT reported a significant reduction in the rate of exacerbations with the Seretide inhaler. The use of rescue medication was significantly lower with Seratide in one RCT. There were no differences between the Symbicort and the Seratide inhalers in two RCTs which reported on asthma symptoms, health related quality of life, or the rate of adverse events. A third RCT reported a significant reduction in symptom-free days with Seretide

3.1.8 Summary

The majority of RCTs identified by the Assessment Group were pair-wise comparisons of predominantly the older ICSs (budesonide, beclometasone dipropionate and fluticasone propionate). The Assessment Group considered the ICSs to be equivalent in clinical terms as few of the pair-wise comparisons showed any statistically significant differences between the drugs. RCTs which compared adding a LABA to ICS treatment (compared with ICS alone) reported improved outcomes with combination treatment. Clinical equivalence of combination treatment (ICS plus LABA) with single vs separate inhalers

was reported in RCTs, and RCTs which compared the two combination inhalers (budesonide/formoterol fumarate vs. fluticasone propionate/salmeterol) reported mixed results.

3.2 Cost effectiveness

3.2.1 Manufacturer's cost-effectiveness submissions.

Two models were submitted by the manufacturers. The GSK model is based on symptom-free days as an efficacy endpoint and the AstraZeneca model is based on asthma exacerbations. None of the submissions compare all five of the licensed ICSs (beclometasone dipropionate, budesonide, fluticasone propionate, mometasone furoate and ciclesonide).

Four manufacturers (Altana, Ivax, Meda and Trinity-Chiesi) limited themselves to a single product. These economic submissions assumed equivalent efficacy between the ICSs and included cost minimisation analyses.

It is important to acknowledge that the literature on modelling cost effectiveness in asthma is sparse and it is difficult to structure and populate a model based on the BTS guidelines.

3.2.1.1 GSK (Seretide)

The economic model addressed the cost effectiveness of the following treatment scenarios:

- Seretide (fluticasone propionate/salmeterol) compared with the same or increased dose of ICS in uncontrolled asthma
- Seretide compared with fluticasone propionate and salmeterol using separate inhalers
- Seretide compared with Symbicort (budesonide/formoterol fumarate) delivered using combination inhalers.

Effectiveness was estimated using the proportion of symptom-free days. Alternative therapies were assumed to have similar mortality and toxicity profiles and delivery devices were also assumed to be equivalent.

Table 1 Results of GSK model

	Dose of ICS					
Comparison	**Low dose**	**Medium dose**	**High dose**	**Low vs medium dose**	**Medium vs high dose**	**High vs low dose**
FP/SAL vs ICS alone	ICER £6,350 to £20,151 per QALY	ICER £12,100 to £24,020 per QALY	ICER £3,660 to £50,017 per QALY	ICER £51 to £15,997 per QALY or FP/SAL dominates	FP/SAL dominates to ICER £14,567 per QALY	NA
FP/SAL combination vs ICS+LABA separates	ICER (for separates) £16,519 to £59,442 per QALY	FP/SAL combination dominates separates	Separates dominate or ICER (for separates) >£166,000 per QALY	NA	NA	NA
FP/SAL vs BUD/FF	FP/SAL cost saving -£183 to +£149	NA	NA	FP/SAL dominates or cost saving -£18	Cost saving -£357	Cost saving -$431 to -£164

FP: fluticasone propionate

SAL: salmeterol

BUD: budesonide

FF: formoterol fumarate

The GSK model is essentially a spreadsheet calculation with no disease progression or transition between states. Although the model has a nominal 1-year time horizon, in effect it is a cross-sectional snapshot of asthma. Using symptom-free days as the effectiveness measure does not give a full reflection of the effectiveness of the treatments and simplifies the disease process. The method of calculating costs was not transparent and the costs appeared low.

3.2.1.2 AstraZeneca (Pulmicort/Symbicort)

Pulmicort (budesonide) was assumed to be cost effective as it is clinically equivalent to other ICSs and the cost of maintenance doses lies within the range calculated for its comparators.

For the evaluation of Symbicort (budesonide/formoterol fumarate) the model was based on the effectiveness of the inhaler at preventing exacerbations.

Each exacerbation was assumed to last for 1 week of a 4 week cycle and the model horizon was 1 year. The model included the costs of medication, consultations and hospital care.

Results showed that Symbicort dominates ICS and LABA administered using separate inhalers as the benefits are equivalent at a lower cost. Symbicort also dominates Seretide as its marginally higher acquisition costs are offset by healthcare savings due to exacerbations prevented. When compared to ICS alone, Symbicort produced an ICER of £40,200 per QALY gained, which is equivalent to £3,700 per exacerbation avoided.

Symbicort may also be used in other therapeutic regimens - adjustable maintenance dosing (AMD) and Symbicort as maintenance and reliever therapy (SMART). The manufacturer's calculations lead them to conclude that these regimens produce a better clinical outcome than the fixed dose regimen and also are more cost effective. However these regimens are currently not within the BTS guidelines.

The Assessment Group felt the model's focus on exacerbations may not capture other important aspects of asthma control. Additionally, the method of deriving comparator costs and relative treatment effect was not transparent. The model results in Symbicort dominating Seretide but this is a result of a small QALY gain and a small cost difference.

3.2.1.3 Altana (Ciclesonide)

No formal cost effectiveness calculations were presented, however, the cost of ciclesonide is within the range of fluticasone propionate, budesonide and beclometasone dipropionate. The manufacturer stated it is cheaper than the combination inhalers Seretide and Symbicort and that ciclesonide would result in cost savings if its use improved compliance and therefore effectiveness and prevented inappropriate use of combination therapies at step 2 of the BTS guidelines. The cost of ciclesonide is compared with combination inhalers without any discussion of their relative effectiveness.

3.2.1.4 Ivax (Qvar)

The submission discusses three published studies. The first compared Qvar (hydrofluoroalkane-propelled beclometasone dipropionate) to beclometasone dipropionate (CFC pMDI) and used data collected from a 1-year pragmatic, international RCT. Costs included study drugs and rescue medications, routine GP visits and costs associated with exacerbations. Total healthcare costs and drug costs were similar for both groups, but Qvar dominated beclometasone dipropionate because the average cost for clinically significant improvement was lower.

Two further studies compared Qvar with hydrofluoroalkane-propelled fluticasone propionate and budesonide Turbohaler (Pulmicort). Both studies were of 8 weeks duration and the main outcome was symptom-free days. Total healthcare costs were lower with Qvar and it dominated budesonide Turbohaler (Pulmicort). Qvar was at least as effective as hydrofluoroalkane-propelled fluticasone propionate at a lower cost. The resource-use data came from a number of countries where asthma management may vary from that used within the UK NHS.

3.2.1.5 Meda (Novolizer)

As the Novolizer is assumed to be at least as effective as the Turbohaler (AstraZenica, budesonide [Pulmicort] DPI) a cost minimisation analysis is briefly presented in the submission. Only drug acquisition costs are considered and at typical doses, Novolizer is cost saving relative to the Turbohaler. This appears to be because the Novolizer inhaler has a refill option while the Pulmicort Turbohaler is not reusable. The submission also points out that improved technique and compliance with the inhaler device would prevent progression in the BTS guideline steps, and would therefore be cost saving. The submission deals mainly with the device and is therefore beyond the scope of this appraisal. However it does emphasise the importance of inhaler device in the overall effectiveness of ICSs.

3.2.1.6 Trinity Chiesi (Pulvinal, Clenil Modulite)

The submission compares the costs of Pulvinal to other DPIs and identifies potential savings. It makes the point that improved compliance with the device will lead to overall savings.

Clenil Modulite is compared to the only non-CFC beclometasone dipropionate on the market (Qvar) in a cost-minimisation analysis. Other than the costs of the drugs themselves the other category of costs that is assumed to vary is that of the therapeutic reviews. As Qvar is not dose equivalent to current beclometasone dipropionate-containing inhalers, half the quantity of Qvar is needed to ensure adequate asthma control.

As Clenil Modulite is dose equivalent to CFC-containing beclometasone dipropionate inhalers the manufacturer argues that there is no requirement for therapeutic review when switching from a standard CFC-containing pMDI. Clenil Modulite saves £0.74 per patient per year in drug costs and £30 is saved by avoiding a therapeutic review, compared with Qvar. However, this is a one-off cost and a short-term benefit in savings as the price difference between the drugs is negligible.

3.2.2 Assessment Group Economic Analyses

The Assessment Group considered the cost effectiveness of five different treatment scenarios within the context of the BTS guidelines:

- a comparison of ICSs at low doses (step 2)
- a comparison of ICSs at high doses (step 4)
- adding a LABA to ICS treatment
- combination treatment (ICS plus a LABA) delivered via single or separate inhalers (step 3)
- a comparison of fluticasone propionate/salmeterol and budesonide/formoterol fumarate combination inhalers.

Where the clinical review showed no consistent evidence of differential effectiveness, a cost comparison was undertaken. Where the clinical evidence

showed systematic differences in effectiveness, a cost consequence analysis was undertaken.

An important issue in the analysis was the derivation of a single representative cost for each ICS because there are many valid methods by which this can be achieved. The mean annual cost for each type of ICS per patient was calculated based on the BTS guidelines and assumptions as to how these doses could be achieved. For each ICS, an unweighted mean annual cost of the various preparations was calculated. A weighted average, determined by 2005 market share, was also calculated. In addition, for each ICS at each of three dose levels, the weighted and unweighted mean annual cost was calculated for:

- all CFC-propelled (pMDI) products
- all hydrofluoroalkane -propelled (pMDI) products
- all dry powder inhaler products
- all relevant products for that ICS (including CFC-containing products)
- all relevant products for that ICS (excluding CFC-containing products).

3.2.2.1 Which is the cheapest ICS drug at BTS treatment step 2? (TAR page 387-392)

At a low dose (400 micrograms beclometasone dipropionate-CFC equivalent per day) beclometasone dipropionate is currently the cheapest ICS, costing an average of £62 per year (weighted mean) or £65 per year (unweighted mean). If CFC containing products are excluded, beclometasone dipropionate still remains the cheapest although it does become more costly. Excluding CFC-containing inhalers has no effect on the price of fluticasone propionate, ciclesonide or mometasone furoate as these are only available in CFC-free inhalers. Fluticasone propionate and mometasone furoate are the most expensive ICS preparations at this dosage.

At the higher dose (800 micrograms beclometasone dipropionate-CFC equivalent per day) beclometasone dipropionate remains the cheapest preparation with a mean cost of £157 per year (weighted) and £130 per year (unweighted). If CFC-containing products are excluded beclometasone

dipropionate is the cheapest by unweighted mean cost, but fluticasone propionate is the cheapest if the weighted mean is used. At the higher dosage mometasone furoate and budesonide are the most expensive preparations.

3.2.2.2 What is the cheapest ICS at step 4 (high dose ICS)? (TAR page 393-397)

At the high dose (1500-1600 micrograms beclometasone dipropionate-CFC equivalent per day) beclometasone dipropionate is the cheapest ICS, costing £260 per year (weighted mean) and £198 per year (unweighted mean). When CFC-containing products are excluded, fluticasone propionate becomes the cheapest available ICS using the weighted mean for yearly costs. At this dose level, budesonide is the most expensive ICS.

It must be emphasised that there is a wide variation in the costs of individual products made using each ICS drug.

3.2.2.3 Which is more cost-effective: to increase the dose of ICS alone or to add a LABA to treatment with a lower dose of ICS? (TAR page 397-405)

This question is addressed by a cost comparison analysis. Of the two RCTs which compared the fluticasone propionate/salmeterol combination with a higher dose of fluticasone propionate, only one showed a statistically significant difference in any outcome (FEV1) favouring the combination. The cost of the combination was £35 less than the cost of the higher dose of the ICS, and £92 less than the cost of the ICS at the lower dose.

In three RCTs, the fluticasone propionate/salmeterol combination showed improvements in lung function (PEFR) and symptom control compared with a higher dose of budesonide. The cost of the combination varied from £94 less than budesonide to £109 more than budesonide using products equivalent to those used in the RCTs.

The budesonide/formoterol fumarate combination is compared to a higher dose fluticasone propionate in one RCT and a higher dose budesonide in four

RCTs. The combination treatment results in improved lung function (PEFR) and better symptom control than a higher dose of ICS alone. The combined inhaler can cost from £163 less than the ICS inhaler to £66 more.

No evidence for comparison with other ICS preparations was available. The Assessment Group noted that small and uncertain differences in treatment effectiveness and considerable variations in product costs within each drug type introduce uncertainty and that conventional rules for judging cost effectiveness are inappropriate.

3.2.2.4 Combination versus separate inhalers at step 3. (TAR page 405-407)

There is no consistent evidence of differential effectiveness. The budesonide/formoterol fumarate combination is always cheaper than taking the drugs in separate inhalers, saving between £36 and £227 per year. Similarly, the fluticasone propionate/salmeterol combined inhaler is always cheaper than taking the drugs separately, saving between £85 and £298 per year. The combinations were not compared to separate inhalers which deliver other ICS preparations (for example, beclometasone dipropionate).

3.2.2.5 Fluticasone propionate/salmeterol vs budesonide/formoterol fumarate at step 3 (TAR page 407-408)

Clinical equivalence was assumed. In making the comparison it was assumed that budesonide 400 micrograms and 800 micrograms was equivalent to fluticasone propionate 200 micrograms and 500 micrograms and that formoterol fumarate 12 micrograms was equivalent to salmeterol 100 micrograms, to reflect dosages used in the RCTs.

At the lower dose level the budesonide/formoterol fumarate dry powder inhaler was the cheapest option costing £231 per year. The cheapest fluticasone propionate/salmeterol combination was a pMDI costing £237 per year.

At the higher dose the cheapest combined preparation was the fluticasone propionate/salmeterol dry powder inhaler costing £446 per year and the

cheapest budesonide/formoterol fumarate combination was the dry powder inhaler costing £462 per year.

The Assessment Group cautioned that the weighted averages conceal a wide variation in the cost of individual preparations of each drug. Usage will also change as CFC-containing products are withdrawn.

4 Issues for consideration

If all ICSs (low and high dose) used alone for the treatment of asthma are equally effective, should the cheapest, or at least the cheapest version of any delivery device-type, be recommended?

Short-duration RCTs (many being of 12 weeks duration) may not predict long-term clinical outcomes.

External validity of the RCTs – consultees note that only 5% of people with asthma seen in general practice would fulfil the eligibility criteria of RCTs.

To what extent does the delivery device affect effectiveness of the ICS, and are different delivery devices appropriate for different groups of patients?

What place should patient preference play in the choice of ICS/delivery device?

Consultees considered the improved control of asthma to be crucial to this appraisal.

5 Ongoing research

None

6 Authors

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March 2007

Appendix A: Sources of evidence considered in the preparation of the overview

A The Assessment Report: Shepherd J, Rogers G, Anderson R et al. (Peninsula Technology Assessment Group [PenTAG)). 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 Submissions from the following organisations:

I Manufacturers/sponsors:

- Glaxosmithkline UK
- AstraZeneca UK Ltd
- Altana Pharma Ltd
- IVAX Pharmaceuticals UK Ltd
- Meda Pharmaceuticals Ltd
- Trinity Pharmaceuticals Ltd

II Professional/specialist and patient/carer groups:

- Action Against Allergy
- British Lung Foundation
- British Thoracic Society
- Education for Health
- General Practice Airways Group
- Asthma UK
- Royal College of Physicians

III Commentator organisations (without the right of appeal):

None

C Additional references used:

None

Appendix B: Summary of the technologies

Proprietary name	Device type	Manufacturer	Dose (micrograms)	Acquisition cost (BNF)
Beclometasone dipropionate (BDP)				
Aerobec autohaler	pMDI	3M Healthcare	50	200 doses £4.04
	pMDI	3M Healthcare	100	200 doses £7.66
Aerobec Forte autohaler	pMDI	3M Healthcare	250	200 doses 16.76
Asmabec Clickhaler	DPI	UCB	50	200 doses = £6.68
	DPI	UCB	100	200 doses = £9.81
	DPI	UCB	250	100 doses = 12.31
Beclazone Easi-Breathe	pMDI	IVAX	50	200 doses = £ 4.34
	pMDI	IVAX	100	200 doses = £ 10.30
Beclazone inhaler	pMDI	IVAX	50	200 doses = £ 1.76
	pMDI	IVAX	100	200 doses = £2.76
	pMDI	IVAX	200	200 doses = £8.11
Beclazone 250-inhaler	pMDI	IVAX	250	200 doses = £6.96
Beclazone 250 Easi-Breathe	pMDI	IVAX	250	200 doses = £20.25
Becloforte	pMDI	A + H / GSK	250	200 doses = £6.99
Beclometasone	pMDI	A + H / GSK	50	200 doses = £4.44
	pMDI	A + H / GSK	100	200 doses = £6.05
	pMDI	A + H / GSK	250	200 doses = £13.95
Becodisks	breath pMDI	A + H / GSK	100	15x 8 refill = £11.42
	breath pMDI	A + H / GSK	200	15x 8 refill = £22.28
	breath pMDI	A + H / GSK	400	15x 8 refill = £44.57
Becotide	pMDI	A + H / GSK	50	200 doses = £1.79
	pMDI	A + H / GSK	100	200 doses = £2.79
	pMDI	A + H / GSK	200	200 doses = £8.14
Clenil Modulite	CFC free pMDI	Trinity - Chiesi	50	200 doses = £3.85
	CFC free pMDI	Trinity - Chiesi	100	200 doses = £7.72
	CFC free pMDI	Trinity - Chiesi	200	200 doses = £16.83
	CFC free pMDI	Trinity - Chiesi	250	200 doses = £16.95
Easyhaler Beclometasone	DPI	Ranbaxy	200	200 doses = £15.60
Filair	pMDI	3M Healthcare	50	200 doses = £3.85
	pMDI	3M Healthcare	100	200 doses = £7.32
Filair Forte	pMDI	3M Healthcare	250	200 doses = £16.01
Pulvinal Beclometasone	DPI	Trinity - Chiesi	100	100 doses = £5.58
	DPI	Trinity - Chiesi	200	100 doses = £10.29
	DPI	Trinity - Chiesi	400	100 doses = £20.41
Qvar	CFC free pMDI	IVAX	50	200 doses = £7.87
	CFC free pMDI	IVAX	100	200 doses = £17.21
Qvar Autohaler	CFC free pMDI	IVAX	50	200 doses = £7.87
	CFC free pMDI	IVAX	100	200 doses = £17.21
Qvar Easi-Breathe	CFC free pMDI	IVAX	50	200 doses = £7.74
	CFC free pMDI	IVAX	100	200 doses = £16.95
Budesonide				
Easyhaler Budesonide	DPI	Ranbaxy	100	200 doses = £9.25
	DPI	Ranbaxy	200	200 doses = £18.50
	DPI	Ranbaxy	400	100 doses = £18.50

Proprietary name	Device type	Manufacturer	Dose (micrograms)	Acquisition cost (BNF)
Novolizer Budesonide	DPI	Meda	200	100 doses = £14.86 (cartridge + inhaler)
	DPI	Meda	200	100 doses = £9.59 (refill only)
Pulmicort	pMDI	AstraZeneca	100	200 doses = £18.50
	pMDI	AstraZeneca	200	100 doses = £18.50
	pMDI	AstraZeneca	400	50 doses = £18.50
Pulmicort inhaler	pMDI	AstraZeneca	200	200 doses = £20.90
Pulmicort L.S.	pMDI	AstraZeneca	50	200 doses = £7.33
Ciclesonide(				
Alvesco	CFC free pMDI	Altana	80	120 doses = £28.56
	CFC free pMDI	Altana	160	60 doses = £16.80
	CFC free pMDI	Altana	160	120 doses = £33.60
Fluticasone propionate				
Flixotide Diskhaler	DPI	A + H / GSK	50	15 x 4 blisters = £8.17
	DPI	A + H / GSK	100	15 x 4 blisters = £12.71
	DPI	A + H / GSK	250	15 x 4 blisters = £24.11
	DPI	A + H / GSK	500	15 x 4 blisters = £40.05
Flixotide Accuhaler	breath pMDI	A + H / GSK	50	60 doses = £6.38
	breath pMDI	A + H / GSK	100	60 doses = £8.93
	breath pMDI	A + H / GSK	250	60 doses = £21.26
	breath pMDI	A + H / GSK	500	60 doses = £36.14
Flixotide Evohaler	CFC free pMDI	A + H / GSK	50	120 doses = £5.44
	CFC free pMDI	A + H / GSK	125	120 doses = £21.26
	CFC free pMDI	A + H / GSK	250	120 doses = £36.14
Mometasone				
Asmanex Twisthaler	DPI	Schering-Plough	200	60 doses = £24.00
	DPI	Schering-Plough	400	60 doses = £36.75
Formoterol fumarate+ budesonide				
Symbicort 100/6	DPI	AstraZeneca	100 (ICS)	120 doses = £33.00
Symbicort 200/6	DPI	AstraZeneca	200 (ICS)	120 doses = £38.00
Salmeterol + fluticasone propionate				
Seretide Accuhaler	breath pMDI	A + H / GSK	100 (ICS)	60 doses = £31.19
	breath pMDI	A + H / GSK	250 (ICS)	60 doses = £36.65
	breath pMDI	A + H / GSK	500 (ICS)	60 doses = £40.92
Seretide Evohaler	CFC free pMDI	A + H / GSK	50 (ICS)	120 doses + £18.14
	CFC free pMDI	A + H / GSK	125 (ICS)	120 doses + £36.65
	CFC free pMDI	A + H / GSK	250 (ICS)	120 doses + £62.29

N.B. All DPI inhalers are breath actuated. Acquisition cost does not include VAT.

Appendix B: Summary of the technologies (correction)

Proprietary name	Device type	Manufacturer	Dose (micrograms)	Acquisition cost (MIMS March 2007)
Beclometasone dipropionate (BDP)				
AeroBec Autohaler	Breath-actuated pMDI	3M Healthcare	50	200 doses £4.04
	Breath-actuated pMDI	3M Healthcare	100	200 doses £7.66
AeroBec Forte Autohaler	Breath-actuated pMDI	3M Healthcare	250	200 doses £16.76
Asmabec	DPI	UCB	50	200 doses £6.68
Clickhaler	DPI	UCB	100	200 doses £9.81
	DPI	UCB	250	100 doses £12.31
Beclazone Easi-Breathe	Breath-actuated pMDI	IVAX	50	200 doses £ 4.34
	Breath-actuated pMDI	IVAX	100	200 doses £10.30
	Breath-actuated pMDI	IVAX	250	200 doses £20.25
Beclazone inhaler	pMDI	IVAX	50	200 doses £ 1.76
	pMDI	IVAX	100	200 doses £2.76
	pMDI	IVAX	200	200 doses £8.11
	pMDI	IVAX	250	200 doses £6.96
Becloforte	pMDI	A + H / GSK	250	200 doses £6.99
Beclometasone	pMDI	non proprietary	50	200 doses £4.44
	pMDI	non proprietary	100	200 doses £6.05
	pMDI	non proprietary	250	200 doses £13.95
Becodisks	DPI	A + H / GSK	100	15x 8 refill £11.42
	DPI	A + H / GSK	200	15x 8 refill £22.28
	DPI	A + H / GSK	400	15x 8 refill £44.57
Becotide	pMDI	A + H / GSK	50	200 doses £1.79
	pMDI	A + H / GSK	100	200 doses £2.79
	pMDI	A + H / GSK	200	200 doses £8.14
Clenil Modulite	CFC-free pMDI	Trinity - Chiesi	50	200 doses £3.85
	CFC-free pMDI	Trinity - Chiesi	100	200 doses £7.72
	CFC-free pMDI	Trinity - Chiesi	200	200 doses £16.83
	CFC-free pMDI	Trinity - Chiesi	250	200 doses £16.95
Easyhaler Beclometasone	DPI	Ranbaxy	200	200 doses £15.60
Filair	pMDI	3M Health care	50	200 doses £3.85
	pMDI	3M Health care	100	200 doses £7.32
Filair Forte	pMDI	3M Health care	250	200 doses £16.01
Pulvinal Beclometasone	DPI	Trinity - Chiesi	100	100 doses £5.58
	DPI	Trinity - Chiesi	200	100 doses £10.29
	DPI	Trinity - Chiesi	400	100 doses £20.41
Qvar	CFC-free pMDI	IVAX	50	200 doses £7.87
	CFC-free pMDI	IVAX	100	200 doses £17.21
Qvar Autohaler	Breath-actuated CFC-free pMDI	IVAX	50	200 doses £7.87
	Breath-actuated CFC-free pMDI	IVAX	100	200 doses £17.21
Qvar Easi-Breathe	Breath-actuated CFC-free pMDI	IVAX	50	200 doses £7.74
	Breath-actuated CFC-free pMDI	IVAX	100	200 doses £16.95
Budesonide				
Easyhaler Budesonide	DPI	Ranbaxy	100	200 doses £9.25
	DPI	Ranbaxy	200	200 doses £18.50
	DPI	Ranbaxy	400	100 doses £18.50

Proprietary name	Device type	Manufacturer	Dose (micrograms)	Acquisition cost (MIMS March 2007)
Novolizer Budesonide	DPI	Meda	200	100 doses £14.86 (cartridge + inhaler) 100 dose refill £9.59
Pulmicort	DPI	AstraZeneca	100	200 doses £18.50
Turbohaler	DPI	AstraZeneca	200	100 doses £18.50
	DPI	AstraZeneca	400	50 doses £18.50
Pulmicort inhaler	pMDI	AstraZeneca	200	200 doses £20.90
Pulmicort L.S.	pMDI	AstraZeneca	50	200 doses £7.33
Ciclesonide				
Alvesco	CFC-free pMDI	Altana	80	120 doses £28.56
	CFC-free pMDI	Altana	160	60 doses £16.80
	CFC-free pMDI	Altana	160	120 doses £33.60
Fluticasone propionate				
Flixotide Diskhaler	DPI	A + H / GSK	50	15 x 4 refill £7.64
	DPI	A + H / GSK	100	15 x 4 refill £12.18
	DPI	A + H / GSK	250	15 x 4 refill £23.58
	DPI	A + H / GSK	500	15 x 4 refill £39.52
Flixotide Accuhaler	DPI	A + H / GSK	50	60 doses £6.38
	DPI	A + H / GSK	100	60 doses £8.93
	DPI	A + H / GSK	250	60 doses £21.26
	DPI	A + H / GSK	500	60 doses £36.14
Flixotide Evohaler	CFC free pMDI	A + H / GSK	50	120 doses £5.44
	CFC free pMDI	A + H / GSK	125	120 doses £21.26
	CFC free pMDI	A + H / GSK	250	120 doses £36.14
Mometasone				
Asmanex Twisthaler	DPI	Schering-Plough	200	60 doses £24.00
	DPI	Schering-Plough	400	60 doses £36.75
Formoterol fumarate+ budesonide				
Symbicort 100/6 Turbohaler	DPI	AstraZeneca	100 (ICS)	120 doses £33.00
Symbicort 200/6 Turbohaler	DPI	AstraZeneca	200 (ICS)	120 doses £38.00
Salmeterol + fluticasone propionate				
Seretide Accuhaler	DPI	A + H / GSK	100 (ICS)	60 doses £31.19
	DPI	A + H / GSK	250 (ICS)	60 doses £36.65
	DPI	A + H / GSK	500 (ICS)	60 doses £40.92
Seretide Evohaler	CFC-free pMDI	A + H / GSK	50 (ICS)	120 doses £18.14
	CFC-free pMDI	A + H / GSK	125 (ICS)	120 doses £36.65
	CFC-free pMDI	A + H / GSK	250 (ICS)	120 doses £62.29

N.B. All DPI inhalers are breath actuated. Acquisition cost does not include VAT.