



The clinical effectiveness and cost-effectiveness of corticosteroids for the treatment of chronic asthma in children under the age of 12 years

Submission of evidence from AstraZeneca UK Ltd regarding the inhaled corticosteroid budesonide (Pulmicort[®]) and budesonide/formoterol combination treatment (Symbicort[®])

This document contains all the relevant evidence in the possession of AstraZeneca UK Ltd related to the appraisal of corticosteroids

EXECUTIVE SUMMARY

Asthma is a considerable burden to the National Health Service (NHS). The management of asthma involves a wide range of services including primary care, hospital inpatients, outpatient care, routine follow up, patient education and advice, emergency visits and prescribed drugs. The annual cost to the NHS of diagnosed asthma in childhood is currently estimated to be £254 million.

Childhood asthma is a complex condition and due to the variety of factors that underlie each individual's asthma, the treatment needs to be considered and managed on an individual basis. The current estimated prevalence rate for asthma in children ranges from 12.5% to 15.5% with prevalence rates higher in boys than girls and prevalence in children over five years of age increasing.

When treating asthma in children under 12 years of age national guidelines state that the main aims are the control of symptoms, including exercise-induced asthma, prevention of exacerbations and the achievement of the best pulmonary function, with minimal side-effects. Inhaled therapy delivering bronchodilator and corticosteroids in various doses is the mainstay of treatment. Inhaled corticosteroids (ICS's), such as budesonide (BUD), are the most effective preventer drug for achieving overall goals for persistent asthma. Due to the highly variable nature of asthma, in order to maintain optimal asthma control, treatment needs to be considered and managed on an individual basis.

A number of ICS's are available and in delivering treatment the drug and inhaler delivery device are inextricably linked with the choice of the most appropriate inhaler device influencing the decision regarding treatment choice. In selecting an inhaler the patient's preference for and ability to use one inhaler over another is essential in ensuring maximum efficiency is attained. Patients also have a preference for simplified treatment with a single inhaler containing preventer and reliever therapy being preferred.

The use of combination inhalers which combine an ICS and a long acting β_2 -agonist (LABA) have the potential to meet patient preferences with the potential to improve compliance. In addition the use of such inhalers ensures that patients increase both their intake of both ICS and LABA at the onset of deterioration of asthma and avoids patients neglecting their ICS in favour of their reliever therapy.

Within the UK budesonide (BUD), from AstraZeneca, for the treatment of asthma is available as Pulmicort and in combination with formoterol as Symbicort.

BUD offers high airway selectivity due to the high intrinsic activity in the airways and a favourable pharmacokinetics profile, which combines low oral availability and rapid clearance elimination from systemic tissues. In contrast to other ICS's (fluticasone propionate, mometasone furoate and ciclesonide) BUD is water soluble a property which minimises the risk of systemic accumulation. *In vivo* BUD undergoes reversible esterification to long chain fatty acids, effectively forming an intracellular depot of the drug. Esterification is partly responsible for both the high selectivity of BUD for the airway epithelium and its long retention in the airways making BUD an ideal candidate for once daily dosing.

Pulmicort

Pulmicort can be administered to paediatric patients via Turbohaler (a dry powder inhaler – DPI), pMDI (pressurised metered dose inhaler) or a nebuliser. Administration via nebuliser is an ideal delivery system for children under two years

of age, while pMDI or Turbohaler DPI are the preferred delivery systems for children over two years of age.

In children under 12 years of age the recommended daily dose of Pulmicort via Turbohaler is 200-800µg/day with the option to adjust dose according to asthma symptoms. Within this dose range Pulmicort demonstrates a clear dose response curve. The dose responsiveness of Pulmicort provides clinicians and patients the opportunity to match treatment to the variable nature of the patient's asthma. In patients maintained on low dose Pulmicort (200µg/day) the use of high dose Pulmicort (800µg/day) has been demonstrated to be effective in treating exacerbations with this dose stepped down once asthma control is achieved. Pulmicort also has the advantage that it can be given as a once or twice-daily regimen. For the same daily dose the two regimens are comparable in achieving and maintaining asthma control. BUD is the only ICS to have been approved for once daily administration in asthma.

In addition, early intervention with Pulmicort improves asthma control increasing the time to first severe asthma-related event and significantly reduces the level of intervention with other ICS's ($p < 0.001$), with trends towards decreased usage of oral corticosteroids and inhaled short-acting β_2 -agonists (SABAs).

In comparison with the other ICS's beclometasone dipropionate (BDP) and fluticasone propionate (FP):

- ◆ Pulmicort and BDP have equal efficacy on a microgram for microgram basis when delivered via the same inhaler device. However when delivered via Turbohaler DPI Pulmicort results in a higher 24-hour cortisol excretion than BDP via pMDI.
- ◆ Pulmicort via Turbohaler DPI has comparable efficacy to FP via a DPI on a microgram for microgram basis. With regard to systemic activity FP produces a greater suppression of plasma cortisol than the corresponding dose of Pulmicort and a number of reports have described cases of adrenal insufficiency in children receiving high doses of FP.

Pulmicort Safety

Pulmicort is well tolerated. In a three-year real-life, prospective, long-term, international study START (inhaled Steroid Treatment As Regular Therapy in early asthma) the incidence, severity and types of AEs reported for Pulmicort were comparable to those reported for placebo. Treatment with Pulmicort within recommended doses is not associated with any increased risk of systemic or ocular events. While an initial slight reduction in growth velocity is observed with Pulmicort this does not affect children attaining their final adult height.

Symbicort

Symbicort, a combination inhaler of BUD with formoterol fumarate is indicated in children aged six years and older for the regular treatment of asthma where use of a combination (ICS and a LABA) is appropriate i.e. patients not adequately controlled with ICS and 'as needed' inhaled SABA or patients already adequately controlled on both ICS and LABAs. Symbicort is not recommended for children under six years of age.

Symbicort 100/6µg per inhalation has a dose range of two inhalations once or twice a day providing a minimum daily dose of 200/12 and a maximum daily dose of 400/24. It is currently licensed for both fixed dosing (FD) and adjustable maintenance dosing (AMD).

Symbicort FD provides a greater improvement in lung function [FEV₁, morning and evening peak expiratory flow (PEF)] compared to ICS alone. Compared with the monocomponents (BUD and formoterol) delivered via separate inhalers Symbicort offers equivalent efficacy but has the potential to improve compliance due to simplicity of treatment.

By providing clinicians and patients with the option to adjust the dose according to the patient's asthma symptoms Symbicort AMD enables patients to take more control of their asthma and adjust their dose according to their asthma symptoms. Providing such control enables a high proportion of patients to step down their treatment and maintain control at a lower level. Clinical data demonstrates that this dose flexibility reduces the number of inhalations required per day ($p < 0.0001$), reducing steroid load and decreasing the potential for side effects.

Cost-effectiveness of Pulmicort and Symbicort

The acquisition costs of Pulmicort were compared to those of other ICS available for maintenance treatment of asthma in the UK and found to be well within the acceptable range of unit costs.

To estimate the cost-effectiveness of Symbicort compared to other ICS treatments, a probabilistic Markov model was developed. The economic model estimated the costs, QALYs, non-exacerbation months and number of exacerbations associated with each treatment over a one-year period.

The cost and resource use inputs for the model included the number and cost of inhalations of maintenance and reliever medication, as well as the cost of managing mild and severe exacerbations and treatment changes. Patient-level data, head-to-head comparisons and meta-analyses based on clinical trials have been used to establish the relative efficacy of the different treatments. A literature search revealed that there are currently no suitable studies examining the utility values for children with asthma receiving ICS treatment, so a study was undertaken to identify the appropriate utility values for the model health states.

This model demonstrated that Symbicort FD provides equivalent health and clinical benefits to the monocomponents of ICS plus LABA at lower costs. In addition, the model showed that Symbicort AMD provides more benefit at a lower cost than either Symbicort FD or the monocomponents of ICS plus LABA. Limited clinical data were available to inform the comparisons of Symbicort with ICS alone or Seretide.

Wider implications of Symbicort recommendation

Switching 10% of patients a year on monocomponents of ICS plus LABA to Symbicort FD and Symbicort AMD would result in a net budget saving to the NHS of £983,118 over five years. Furthermore, increasing the current proportion of Symbicort patients who receive Symbicort AMD would save the NHS in England and Wales £317,614 over a five-year period, whilst also improving health benefits for paediatric patients.

