The clinical effectiveness and cost-effectiveness of corticosteroids for the treatment of chronic asthma in adults and children aged 12 years and over

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

National asthma guidelines state that goals of treatment include the control of symptoms and the prevention of exacerbation – with minimal side effects. The mainstay of treatment is inhaled therapy delivering bronchodilator and corticosteroid in varying doses. Inhaled corticosteroids (ICS's) are the most effective preventer drug for achieving overall treatment goals for persistent asthma and the aim of treatment is to maintained patients on the lowest dose of ICS. Due to the highly variable nature of asthma, in order to maintain optimal asthma control treatment needs to be flexible and managed on an individual basis.

The SIGN / BTS Guidelines describe a stepwise approach to asthma. These are noted in the scope for this appraisal and are widely accepted by clinicians in the UK. But asthma is also a variable disease with variations over hours, days or even seasons. Patients often have long periods of good control followed by episodes of acute, severe deterioration – exacerbations – which are distressing, even life-threatening, for patients and can have considerable implications for the NHS. AstraZeneca believes that addressing the variable nature of asthma through appropriate management regimes leads to more effective and cost effective health care.

A number of ICSs are available and the choice of the most appropriate is based on a number of key factors of which the delivery device is an important component. The drug and inhaler are inextricably linked. In selecting a particular ICS, patient preference for and ability to use one inhaler over another is essential in ensuring maximum efficiency is attained. Incorporating patient preference in the choice of medication has the potential to aid compliance. Patients have a preference for simplified treatment with a single inhaler containing preventer and reliever therapy preferred.

Combination inhalers, which combine an ICS and long-acting β_2-agonist (LABA), such as Symbicort, have the potential to meet patient preferences and improve compliance whilst also ensuring patients increase their intake of both ICS and LABA at the onset of deterioration of asthma.

Budesonide (BUD) is the most extensively studied ICS. It has been used in the treatment of asthma for over 30 years and has an unsurpassed wealth of data supporting its efficacy and safety and offers a favourable benefit/risk ratio. Within the UK, BUD from AstraZeneca for the treatment of asthma is available as Pulmicort and in combination with formoterol as Symbicort.

Pulmicort
Pulmicort can be administered via Turbohaler (a dry powder inhaler - DPI) or a pressurised metered dose inhaler (pMDI). Pulmicort Turbohaler is suitable for both once daily (od) and twice daily (bd) dosing providing a dose range of 200 to 1,600µg/day.

In addition Pulmicort Respules 0.5mg and 1mg nebuliser suspension are indicted for use in bronchial asthma in patients where the use of a pressurised inhaler or dry powder inhaler is unsatisfactory or inappropriate.

The speed of action of Pulmicort is not well recognised, with improvements in lung function apparent approximately four hours after dosing and detectable as early as one hour after administration. It has a clear dose-response curve with maximum benefits seen with doses between 100-800µg bd and is effective in patients with all degrees of persistent asthma. The dose-responsiveness of Pulmicort provides clinicians and patients with the opportunity to match treatment to the variable nature of the disease. Several studies have demonstrated the dose-responsiveness of BUD, supporting the effectiveness of initial short-term treatment with high doses (800µg bd), maintenance with low doses (100µg bd) and, during maintenance, the effectiveness of early intervention with high doses to treat exacerbations. In addition, early intervention with Pulmicort improves asthma control and long-term outcome.

Pulmicort Safety

Pulmicort has been extensively studied in more than 580 clinical trials, including over 38,000 patients and volunteers. Pulmicort is well tolerated. For example, in a three-year real-life prospective study (START) the incidence, severity and types of adverse events reported for Pulmicort were comparable to those reported for placebo. Pulmicort is the only ICS with such long-term data.

BUD as Pulmicort Turbohaler and Pulmicort Respules is the only ICS to have a pregnancy category rating of B in the US. Evidence for Pulmicort from registry data databases and clinical trials has clearly demonstrated that Pulmicort has no effect on the outcome of pregnancy.

Pulmicort vs. beclometasone dipropionate (BDP) and fluticasone propionate (FP)

Current treatment guidelines assume BDP and Pulmicort to have equal efficacy on a microgram for microgram basis. The comparative effectiveness is, however, dependent upon the delivery device used and when delivered via Turbohaler DPI Pulmicort is more effective than BDP (via pMDI or Diskhaler DPI) on a 2:1 ratio, with asthma control achieved at half the dose.

When delivered via their respective DPI devices BUD and FP demonstrate comparable efficacy on a microgram for microgram basis.

Symbicort

Symbicort, a combination inhaler of BUD with formoterol fumarate, is indicated in the regular treatment of asthma where use of a combination (ICS and LABA) is appropriate i.e. patients not adequately controlled with ICS and "as-needed" inhaled short acting β_2-agonist (SABA), or patients already adequately controlled on both ICS and LABAs.

Symbicort has a dose range of one inhalation twice daily to four inhalations twice daily from a single inhaler resulting in a minimum daily dose of 200/12µg and a maximum daily dose of 1600/48µg. It is currently licensed for both fixed dosing (FD) and adjustable maintenance dosing (AMD) with further indications expected in the future.

Symbicort Efficacy

Symbicort offers equivalent efficacy to the monocomponents via separate inhalers, with the benefit of allowing improved compliance due to simplicity of treatment. Symbicort also offers a more rapid improvement in asthma control with regard to improving peak expiratory flow (PEF) versus separate inhalers ($p<0.07$ following 2-3 weeks of treatment). In addition, compared with single inhalers the use of Symbicort

reduces the number of patients withdrawing from treatment (9.2% vs. 19.4%, p=0.008), suggesting that the use of a single combination inhaler improves adherence to treatment.

The Symbicort FD regimen provides a greater improvement in asthma control compared with ICS/increased-dose ICS alone.

In comparison with the other combination inhaler Seretide, Symbicort FD (800/24µg/day) offers equivalent efficacy to Seretide (100/500µg/day). There is, however, evidence that Symbicort FD reduces the number of hospitalisations compared with Seretide.

In addition to the FD indication, Symbicort is also licensed for adjustable maintenance dosing (Symbicort AMD) in which the dose can be adjusted up or down according to the patient's asthma symptoms. Symbicort is the only combination inhaler which enables patients to adjust their dose according to the variability of their asthma, using an asthma action plan. This avoids the need for a new prescription of a new (strength) inhaler – which is potentially wasteful and introduces delays to treatment adjustment.

When compared with Symbicort FD, Symbicort AMD provides more effective asthma control at a lower (36%) overall ICS dose with a significant reduction in healthcare costs. Furthermore, as Symbicort AMD enables patients to reduce their dosage according to the severity of their asthma symptoms, the number of inhalations required are reduced compared with Symbicort FD and the overall drug load for the patient is minimised.

When compared with Seretide, Symbicort AMD provides mores effective asthma control, reducing exacerbation rates (95% CI 8.3 to 60.3, p=0.018). The number needed to treat (NNT) to avoid one exacerbation over one year for Symbicort AMD vs. Seretide is 4.9.

Cost-Effectiveness – Pulmicort

Unit costs for Pulmicort lie comfortably within the range of unit costs for ICS preparations available in England and Wales.

Cost-Effectiveness – Symbicort

A probabilistic Markov model was developed to estimate the cost-effectiveness of Symbicort compared to ICS alone, the monocomponents of ICS-plus-LABA and to Seretide.

Symbicort FD was shown to provide equivalent benefit at less cost compared to the monocomponents, ICS+LABA. Similarly, Symbicort FD also provided more benefits at a lower cost when compared to Seretide, i.e. Symbicort FD dominated both ICS+LABA and Seretide. Symbicort FD was cost-effective in comparison to ICS alone; the regimen was associated with a cost per additional QALY of approximately £40,000. Adjustable Symbicort regimens provided greater clinical and health benefits at a lower cost when compared to Symbicort FD (i.e. adjustable Symbicort regimens dominated Symbicort FD).

These cost-effectiveness results remained robust when subjected to probabilistic and deterministic sensitivity analysis.

Wider Implications

Switching Step 3 patients from alternative therapies to Symbicort FD and adjustable Symbicort dosing is likely to result in a net budget saving of £1.82 million over the next five years across England and Wales, together with reductions in primary care- and hospital-managed exacerbations of 35,578 and 48,853 respectively.

Switching a proportion of patients on ICS alone to Symbicort would increase patient benefits and would cost the NHS an additional £62.83 million over the next five years. Switching a proportion of patients receiving ICS+LABA in separate inhalers to Symbicort would produce similar health benefits but produce cost savings of £19.53 million in the next five years. Similarly, switching 50% of patients from Seretide to Symbicort would save £38.55 million and would, in tandem, result in improved health outcomes for asthma patients. Implementing all of the suggested Symbicort switch scenarios would be expected to save the NHS approximately £2 million over five years while substantially improving patient care.

Overall Conclusion

The clinical and efficacy data presented in this submission clearly demonstrates that of all the ICSs in current usage, Pulmicort is the most widely studied and its unit cost is well within the range of unit costs for ICS preparations available in England and Wales.

Symbicort offers the advantage of providing ICS and LABA together in the simplicity of one inhaler, together with the advantages of flexible dosing regimes to best suit the individual needs of the patient. Fixed-dose Symbicort offers additional health / clinical benefit at an acceptable increase in cost compared to ICS alone, whilst providing the same or additional health / clinical benefits in a less costly way compared to either ICS plus LABA via separate inhalers (monocomponents), or Seretide. Adjustable-dose Symbicort offers greater health / clinical gain in a less costly manner than fixed dose Symbicort. This means that overall, adjustable dosing with Symbicort offers greater health gains but in a less expensive manner than fixed dose, monocomponents or Seretide. The cost savings and health benefits of an ICS-with-LABA therapy at Step 3 are maximised when patients use the flexible dosing strategies of Symbicort.