Scottish Medicines Consortium

budesonide/formoterol 100/6, 200/6 turbohaler (Symbicort SMART®) No. (362/07)

Astra Zeneca UK Limited

9 March 2007 (*Issued May 2007)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

budesonide/formoterol turbohaler (Symbicort® SMART®) is accepted for use within NHS Scotland, in adults, for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta$_2$-agonist) is appropriate; Symbicort is taken as regular maintenance treatment and as needed in response to symptoms.

In patients using inhaled budesonide/formoterol as preventer therapy, use of the same inhaler for reliever therapy is associated with a longer time to first severe exacerbation than use of comparator reliever regimens. In addition, some patients may be able to reduce the dose of preventer therapy.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

The regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta$_2$-agonist) is appropriate; Symbicort is taken as regular maintenance treatment and as needed in response to symptoms.

Dosing information

Maintenance dose (200/6 formulation): 100mcg budesonide/6mcg formoterol; 200mcg budesonide/6mcg formoterol two inhalations per day, given either as one inhalation in the morning and evening or as two inhalations in either the morning or evening. For some patients a maintenance dose of two inhalations twice daily may be appropriate. Patients should take one additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than six inhalations should be taken on any single occasion.

NB: This indication is also applicable to the 100/6 formulation.

Product availability date

Date to be confirmed

Summary of evidence on comparative efficacy

Budesonide/formoterol turbohaler (Symbicort®) is a combination inhaler containing a corticosteroid and a rapid onset long acting beta$_2$-agonist (LABA). It has been licensed in the UK for asthma maintenance therapy since 2001. Five randomised controlled trials have been conducted which support the use of Symbicort® as a new treatment regimen to provide both maintenance and reliever therapy (Symbicort SMART®).

Three double-blind, randomised parallel-group studies have been conducted which included maintenance treatment with an inhaled corticosteroid (ICS) + LABA as a comparator arm. The studies were conducted in patients with moderate to severe asthma, with a forced expiratory volume in 1 second (FEV_1) in the respective trials of 50-100%, >50% and 60-100% of predicted normal. Patients were required to be on ICS for at least one to three months prior to study entry. The primary endpoint in all trials was the time to first severe exacerbation (defined as deterioration in asthma resulting in emergency treatment or hospitalisation or the need for oral steroids for ≥ 3 days or more, as judged by the investigator) and was analysed using a log-rank test and a Cox proportional hazards model and described using Kaplan Meier curves. Secondary endpoints included rate of exacerbations, mean asthma symptom score, time to first hospitalisation/emergency room treatment, lung function and health-related quality of life measures.

The first trial randomised 3394 patients aged ≥ 12 years, to one of three treatments; budesonide/formoterol turbohaler 200/6µg one inhalation twice daily (bd) + budesonide/formoterol 200/6 µg as needed, budesonide/formoterol 200/6µg turbohaler one inhalation bd + terbutaline 0.5mg turbohaler as needed or budesonide/formoterol turbohaler 200/6µg one inhalation bd + formoterol 6µg turbohaler as needed for 12 months. The efficacy analyses were performed on data from 3382 patients for whom data were recorded after randomisation.

The time to first severe exacerbation was significantly prolonged for the comparisons between budesonide/formoterol for maintenance and relief versus the budesonide/formoterol + formoterol (p=0.0048) or budesonide/formoterol + terbutaline (p< 0.0001) groups. Budesonide/formoterol for maintenance and relief reduced the instantaneous risk of a severe exacerbation by 27% (95% confidence interval [CI] 10, 41%) compared with budesonide/formoterol + formoterol and by 45% (95% CI 32, 55%) compared with budesonide/formoterol + terbutaline. For secondary endpoints of rate of exacerbations, mean asthma symptom score, time to first hospitalisation/emergency room treatment and lung function, budesonide/formoterol for maintenance and relief was consistently superior to budesonide/formoterol + formoterol and budesonide/formoterol + terbutaline groups. However asthma-control days, defined as days without symptoms or reliever use, increased in all groups with no significant between group differences.

In the second trial 2760 patients were randomised to budesonide/formoterol turbohaler 100/6µg bd + budesonide/formoterol 100/6µg turbohaler as needed, budesonide/formoterol turbohaler 100/6µg bd + terbutaline turbohaler 0.5mg as needed or budesonide turbohaler 400µg bd + terbutaline turbohaler 0.5mg as needed. Budesonide/formoterol for maintenance and relief significantly prolonged the time to first severe exacerbation when compared with both comparator groups (p<0.001); the risk of experiencing a severe exacerbation was 45% (hazard ratio [HR] 0.55, 95% CI 0.44, 0.67) and 47% (HR 0.53, 95% CI 0.43, 0.65) lower when compared with the budesonide/formoterol + terbutaline and budesonide + terbutaline groups, respectively. For the secondary endpoints of severe asthma exacerbations requiring medical intervention, time to first, second and third exacerbation requiring medical intervention and improvement in asthma symptoms (nocturnal awakenings and morning peak expiratory flow [PEF]) budesonide/formoterol for maintenance and relief was superior to both comparator groups.

In the third trial, reported in poster form, 3335 patients aged ≥ 12 years were randomised to budesonide/formoterol turbohaler 200/6µg one inhalation bd + budesonide/formoterol 200/6 µg turbohaler as needed, salmeterol/fluticasone evohaler 25/125µg, two inhalations bd + terbutaline turbohaler 0.5mg as needed or budesonide/formoterol turbohaler 400/12µg, one inhalation bd + terbutaline 0.5mg turbohaler as needed for six months. This trial used double maintenance doses in the comparator arms compared with the regimen under review. The time to first severe exacerbation was significantly prolonged for budesonide/formoterol for maintenance and relief versus the budesonide/formoterol + terbutaline (p=0.023) and salmeterol/fluticasone + terbutaline (p< 0.0034) groups. For the secondary endpoint of rate of exacerbations budesonide/formoterol for maintenance and relief was superior to both groups and superior to salmeterol/fluticasone + terbutaline only for rates of hospitalisation/emergency room treatment. Indicators of asthma control (symptoms, night time awakenings, use of as-needed medication and lung function) were similarly improved in all groups.

Two further studies have compared budesonide/formoterol for maintenance and relief with a maintenance treatment of a doubled dose of inhaled corticosteroid. In both trials patients were required to be on ICS for at least three months prior to study entry. The first study recruited 697 patients aged 11-79 years with mild to moderate asthma and a FEV_1 60-100% of predicted normal. Following a 2-week run-in period where patients were treated with inhaled corticosteroids they were randomised to budesonide/formoterol turbohaler 100/6µg two inhalations once daily + budesonide/formoterol turbohaler 100/6µg as needed or budesonide turbohaler 200µg two inhalations once daily + terbutaline turbohaler 0.5mg as needed for six months. The primary efficacy variable was change from baseline in the morning PEF. The mean changes from baseline in morning PEF were 34 and 10L/min for the budesonide/formoterol for maintenance and relief and budesonide + terbutaline groups respectively (p<0.001). The second trial recruited 1890 patients with moderate to severe asthma and a FEV_1 50-90% of predicted normal. Patients were randomised to

budesonide/formoterol 200/6µg turbohaler two inhalations once daily + budesonide/formoterol turbohaler 200/6µg as needed or budesonide turbohaler 200µg two inhalations bd + terbutaline turbohaler 0.5mg as needed for 12 months. The primary efficacy variable, time to first severe exacerbation (defined as hospitalisation/ED treatment due to asthma worsening, the need for oral steroids because of asthma (as judged by the investigator) or a ≥ 30% decrease from baseline in PEF am on 2 consecutive days), was prolonged by budesonide/formoterol for maintenance and relief group compared with the budesonide + terbutaline group.

Summary of evidence on comparative safety

All treatments were well tolerated in the clinical studies. The incidence of pharmacologically predictable adverse events related to treatment with inhaled corticosteroids or beta$_2$-agonists was rare and comparable across treatment groups. Palpitations, tachycardia, hoarseness, oral candidosis and dysphonia were reported in between 0.1% and 2% of patients in the clinical studies. There were nine deaths reported in the six trials and none were considered causally related to treatment. Three serious adverse events (atrial fibrillation and dizziness in one trial and not specified in another trial) were considered causally related to treatment with budesonide/formoterol for maintenance and relief.

Summary of clinical effectiveness issues

The studies described previously have compared the use of budesonide/formoterol for maintenance and reliever therapy with a range of comparator regimens which may be used at steps 2/3 of the Scottish Intercollegiate Guidelines Network (SIGN) and the British Thoracic Society (BTS) British Guideline on the Management of Asthma. Whilst there has been some criticism of some individual trials in terms of the generalisability of results to the whole asthma population, there appears to be evidence of superiority of the proposed regimen compared to a number of alternatives including the use of a SABA when required in addition to, the same and increased maintenance doses of the ICS + LABA regimen, increasing the dose of ICS and use of salmeterol/fluticasone.

Health-related quality of life data was published for two trials. The Asthma Control Questionnaire (five-item version; ACQ-5) includes 5 questions on the burden of symptoms. Health-related quality of life was assessed using a standardised version of the Asthma Quality of Life Questionnaire (AQLQ(S)) consisting of 32 questions. A change in ACQ-5 and AQLQ(S) overall scores of ≥ 0.5 is considered clinical relevant. In the first study, described previously, the adjusted mean change from baseline in the overall ACQ-5 score was statistically superior for the budesonide/formoterol for maintenance and relief vs. both of the comparator arms. However, in an open label study, which compared budesonide/formoterol for maintenance and relief with salmeterol/fluticasone 50/250 µg bd (dose titration allowed) + salbutamol as need, there was no statistically significant difference between groups. Although the adjusted mean changes from baseline in the overall ACQ-5 and AQLQ(S) scores were considered clinically relevant for both groups. There is conflicting evidence of the superiority of the budesonide/formoterol for maintenance and relief regimen in terms of patients' symptomatic improvement as reflected in ACQ-5 and AQLQ scores.

The pivotal trials recruited patients aged 12 years or older. However the indication under review is applicable to patients aged 18 years and older.

Summary of comparative health economic evidence

The manufacturer presented a one-year cost-utility Markov model comparing budesonide/formoterol turbohaler 200/6µg one inhalation bd + budesonide/formoterol 200/6 µg as needed relative to three different asthma therapies. The main data sources were (i) the third trial reported in poster form of 3335 patients aged ≥ 12 years, and (ii) a meta analysis of the two parallel trials against the high dose budesonide turbohaler 200µg. Utilities were based on a separate postal EQ-5D study among asthma sufferers. The main findings were that budesonide/formoterol turbohaler 200/6µg one inhalation bd + budesonide/formoterol 200/6 µg as needed relative to:

- budesonide/formoterol turbohaler 400/12µg one inhalation bd + terbutaline 0.5mg turbohaler as needed was estimated as dominating (i.e. lower overall economic cost and more QALYs)
- salmeterol/fluticasone evohaler 25/125µg two inhalations bd + terbutaline turbohaler 0.5mg as needed was estimated as dominating.
- budesonide turbohaler 200µg two inhalations bd + terbutaline turbohaler 0.5mg as needed was estimated as £4,434 per QALY
- budesonide/formeterol turbohaler 200/6ug one inhalation bd for maintenance plus terbutaline as needed was considered the most appropriate comparator at a QALY of £12,917.

Given these results, the economic case was demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Asthma UK Scotland
Patient Interest Group Submission: British Lung Foundation Scotland

Additional information: guidelines and protocols

The SIGN/BTS issued the British Guideline on the Management of Asthma in May 2004. In adult patients taking inhaled steroids at doses of 200-800µg/day the first choice at step 3 would be the addition of an inhaled LABA.

- The LABA is continued if a good response is obtained.
- The ICS dose is increased to 800µg/day if there if benefit but control is still inadequate.
- The LABA is stopped and the ICS dose is increased to 800µg/day if there is no response.

The National Institute for Health and Clinical Excellence (NICE) are undertaking a technology assessment report entitled inhaled corticosteroids and long acting beta$_2$-agonists for the treatment of chronic asthma in adults and children aged 12 years and over. The expected date of issue is November 2007.

Additional information: comparators

The SIGN/BTS Guideline on the Management of Asthma recommends adding a LABA to ICS (+ short acting beta$_2$-agonist for reliever therapy) at step three of the management ladder.

Additional information: costs

Product	Regimen*	Cost **per year (£)
budesonide/formoterol for maintenance and relief	**budesonide/formoterol 200/6µg one inhalation bd + budesonide/formoterol 200/6ug as needed.**	**346**
budesonide/formoterol + terbutaline as needed	budesonide/formoterol 200/6µg one inhalation bd + terbutaline 0.5mg as needed.	256
budesonide/formoterol + terbutaline as needed	budesonide/formoterol 200/6ug two inhalations bd + terbutaline 0.5mg as needed.	486
salmeterol/fluticasone + terbutaline as needed	salmeterol/fluticasone 25/125 two inhalation bd + terbutaline 0.5mg as needed.	470

***The regimens listed in the table are not exhaustive, due to the number of preparations available and the combinations of these which can be used in practice.*
***Costs are based on two 'as needed' doses given per day in addition to the regular dose (based on the mean number of additional inhalations per day from the first study in the comparative efficacy section).*
Doses are shown for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

Based on the number of patients currently estimated to be suitable for step 3 of the SIGN/BTS Guidelines, the manufacturer estimated an eligible patient population of around 80,000. A range of scenarios were presented to illustrate the potential impact of (Symbicort® maintenance and reliever therapy SMART® regimen) depending on the treatment most likely to be displaced. The market share was assumed to be 8% in year 1 rising to around 40% by year 5. The manufacturer estimated the gross drug cost of the maintenance and reliever therapy regimen including reliever therapy, at £2.1m in year 1 rising to £10.7m in year 5 with corresponding net costs of £3.8m and £12.6m an increase of £8.8mn over the 5 years. However, taking into account the effect on displaced therapies, the net overall impact on drug costs is estimated to be a cost saving of £290k in year 1 and £1.5m in year 5.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 16 March 2007.

Costs in the 'Cost of relevant comparators' section are based on prices available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission.

Rabe KF, Atienza T, Magyar P, Larsson P, et al. (2006) Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 368(9537):744-53

O'Byrne PM, Bisgaard H, Godard PP, et al. (2005) Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 171: 129-136

Kuna P, Peters MJ and Buhl R. (2006) Budesonide/formoterol as maintenance and reliever therapy reduces asthma exacerbations versus a higher maintenance dose of budesonide/formoterol or salmeterol/fluticasone. European Respiratory Journal 28(Suppl 50):205s Abs P1228

Rabe KF, Pizzichini E, Stallberg B, et al. (2006) Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma. Chest 129: 246-256

Scicchitano R, Aalbers R, Ukena D, et al. (2004) Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 20: 1403-1418