salmeterol/fluticasone 50/500 micrograms inhaler  
(Seretide 500 Accuhaler®)  
GlaxoSmithKline

11 February 2008

The Scottish Medicines Consortium 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

salmeterol/fluticasone 50/500 microgram inhaler (Seretide 500 Accuhaler®) is not recommended for use within NHS Scotland for the symptomatic treatment of patients with chronic obstructive airways disease (COPD) with a forced expiratory volume in 1 second (FEV₁) 50% to <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

While there was an improvement in lung function tests and a reduction in both moderate and severe exacerbations with salmeterol/fluticasone in comparison with placebo, there was no difference in mortality rate over 3 years. In addition, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,  
Scottish Medicines Consortium
**Indication**
Symptomatic treatment of patients with chronic obstructive airways disease (COPD) with a forced expiratory volume (FEV₁) <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

**Dosing information**
One inhalation twice daily.

**Product availability date**
July 2007

**Summary of evidence on comparative efficacy**

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is usually progressive, not fully reversible and does not change markedly over several months. The product under review is a combination inhaler containing 50 micrograms salmeterol, a selective, long acting beta2-agonist that acts as a bronchodilator, and 500 micrograms fluticasone, a synthetic corticosteroid with potent anti-inflammatory activity. The formulation is a pre-dispensed dry powder inhaler device (Accuhaler®). This submission concerns an extension of the licence to increase the COPD patient population in which the product is indicated by inclusion of those patients with milder disease; the pre-bronchodilator forced expiratory volume in one second, (FEV₁) threshold is raised from the accepted standard of <50% to <60% predicted. The evidence comes from two trials.

The pivotal, double-blind, randomised, placebo-controlled trial recruited patients aged 40 to 80 years who were current or former smokers with ≥10 pack-year history, diagnosis of COPD, defined as pre-bronchodilator FEV₁ <60% predicted, pre-bronchodilator FEV₁ to forced vital capacity (FVC) ratio ≤ 0.70, and with an increase of <10% predicted FEV₁ on administration of 400 micrograms of salbutamol.

Patients were randomised equally, with stratification for country and smoking status, to receive one of four, twice-daily inhaler treatments: salmeterol/fluticasone 50/500 micrograms (combination treatment), salmeterol 50 micrograms, fluticasone 500 micrograms or placebo. Treatment duration was 3 years with assessments every 12 weeks. Prior to a 2-week run-in period existing corticosteroids and long-acting bronchodilators were stopped. Patients were allowed to continue all other COPD treatment. After exclusion of 72 randomised patients due to deficiencies in trial conduct, the remaining 6112 patients comprised the intention to treat, efficacy analysis population. This included patients who withdrew from the study and subsequently could receive any COPD medication. The trial was powered only to detect changes in the primary outcome of death from any cause for the comparison between combination treatment and placebo.

The proportion (number) of deaths in the placebo, salmeterol, fluticasone and combination groups was; 15% (n=231/1524), 14% (n=205/1521), 16% (n=246/1534) and 13% (n=193/1533), respectively.
After 3 years, there was no significant difference in the proportion of deaths between the combination and placebo groups (hazard ratio (HR) 0.83, 95% confidence intervals (CI) 0.68 to 1.00, p=0.052); or between the combination and salmeterol groups. Analysis of the number of deaths, judged by a blinded committee to be COPD-related, failed to demonstrate any significant improvement with combination therapy compared with either placebo or salmeterol, although there was a significant reduction compared with fluticasone (72 vs 106, respectively, HR 0.67, 95% CI 0.5 to 0.9).

Secondary endpoints included frequency of COPD exacerbations, defined as symptomatic deterioration requiring treatment with antibiotics and/or systemic corticosteroids, (moderate exacerbation), and / or hospitalisation, (severe exacerbation). Sixty-eight to 70% of patients experienced at least one exacerbation while on study treatment. Combination treatment significantly reduced moderate exacerbations compared with all other treatments, but the reduction in severe exacerbations was only significant compared with placebo. Combination treatment significantly increased FEV₁, compared with all other treatments. Health status was assessed in 81% (n=4951/6112) patients using the disease specific St George’s Respiratory Questionnaire (SGRQ). There were no clinically significant differences among treatment groups.

A higher proportion of patients withdrew in the placebo arm, 44% (n=673/1524), than in any of the active treatment arms, with the lowest proportion of withdrawals occurring in the combination arm, 34% (n=522/1533). The most common reason for withdrawal was adverse events, including on-treatment deaths.

Another randomised, double-blind, placebo-controlled trial recruited patients with a history of ≥10 pack-years of smoking, pre-bronchodilator FEV₁ of 25-70% predicted, pre-bronchodilator FEV₁ to FVC ratio ≤ 0.70, increase of <10% of predicted FEV₁ on inhalation of 400mcg salbutamol, chronic bronchitis, at least one episode of acute COPD symptom exacerbation per year in the previous 3 years, at least one exacerbation (that required treatment with oral corticosteroids, antibiotics, or both) in the year prior to the start of the trial. The number of patients randomised equally to the same 4 treatment groups as in the pivotal trial was 1465 and they were treated for a period of one year. During a 2-week run-in, existing corticosteroids and long-acting beta2-agonists were discontinued. Other COPD treatments were allowed.

The primary outcome measure of pre-treatment FEV₁ was significantly increased by all active treatments compared with placebo. At the end of the trial, pretreatment FEV₁ in the combination group had increased by 10% compared with 2% in both the salmeterol and fluticasone groups, and had fallen by 3% in the placebo group.

The combination treatment produced significant improvements compared with all other treatments in the secondary outcomes of other lung function tests, breathlessness and relief bronchodilator use. The combination treatment significantly reduced the exacerbation rate compared with placebo; however there was no significant difference when compared with the two other active treatments. The number of night-time awakenings fell significantly in the combination group, compared to placebo and salmeterol, but not to fluticasone. Only the combination treatment group produced a clinically significant improvement in health status, measured using the SGRQ questionnaire. The difference compared with placebo was 2 points on a 100-point scale.

Significantly fewer patients withdrew from the combination (89/358; 25%) and fluticasone (108/374; 29%) groups than from the placebo (140/361; 39%) and salmeterol (119/372; 32%) groups.

*Other data were also assessed but remain commercially confidential.*
**Summary of evidence on comparative safety**

In the pivotal trial, rates of pneumonia were significantly higher in the groups that received treatments containing fluticasone. The probability of having pneumonia as an adverse event during the 3-year period was 20%, 18%, 13% and 12% for the combination treatment, fluticasone, salmeterol and placebo respectively. The numbers of on-treatment deaths from pneumonia were 8, 13, 9 and 7 for the combination treatment, fluticasone, salmeterol and placebo respectively.

Adverse events that led to premature study drug discontinuation occurred in 18% (n=272/1546) patients in the combination treatment group, compared with 23% (n=356/1552) in the fluticasone, 20% (n=315/1542) in the salmeterol and 24% (n=367/1544) in the placebo groups. COPD was the adverse event that most commonly led to premature study drug discontinuation.

There was an expected increase in local oropharyngeal effects with the corticosteroid-containing treatments.

**Summary of clinical effectiveness issues**

The primary outcome in the pivotal trial was the comparison of all-cause mortality between the combination treatment group and the placebo group. However, 59% of patients assigned to treatment with placebo were required to discontinue their existing treatment with inhaled long-acting bronchodilators and/or corticosteroids at study entry. Therefore, it is possible that this group received sub-optimal therapy and may have contributed to the high withdrawal rate in the placebo group. It might also be expected that these patients were more likely to experience worse outcomes such as exacerbations. However, after withdrawal, patients could receive any COPD medication and still be included in the ITT analysis. In practice in Scotland, it is likely that a substantial proportion of this patient population would be receiving long-acting bronchodilators and/or corticosteroids for the treatment of COPD.

As the primary endpoint did not reach statistical significance, changes in secondary outcomes should be considered with caution. Also the post-hoc analysis of subgroups according to FEV\textsubscript{1} status was not sufficiently powered to detect changes in any outcomes between treatment groups.

An important safety finding in the pivotal trial was the excess of patients who developed pneumonia among those receiving study medications containing fluticasone.

It is not clear from the evidence submitted that COPD patients with FEV\textsubscript{1} in the range 50 to <60% would benefit from combination treatment with inhaled long-acting beta2-agonists and corticosteroids.
Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing treatment with salmeterol/fluticasone with salmeterol, fluticasone and placebo, for patients with COPD and an FEV\(_1\) < 60% predicted. The main data source was the pivotal clinical trial and 4 regression models were used to estimate survival, utilities, study drug costs and other costs. The manufacturer estimated incremental cost per QALY ratios of £13k, £9k and £3k for the comparisons with placebo, salmeterol and fluticasone respectively. A post-hoc sub-group analysis of patients with an FEV\(_1\) of 50% to 60% predicted, resulted in cost per QALY estimates of £15k, £8k and £3k.

The main concern with the economic evaluation was the lack of transparency. Initially, it was difficult to validate the models used as very few data were provided. In addition, it was unclear why 4 different models were used to predict survival, utilities, and costs when 3-year trial data were available and no extrapolation beyond the end of the clinical trial was carried out. The manufacturer explained the need for modelling due to the high withdrawal rate in the clinical trial and subsequently provided some additional analyses based on the raw data from the clinical trial in order to provide some reassurance that the model estimates were reasonable. For patients with an FEV\(_1\) < 60% predicted, the cost per QALY estimates based on the trial data alone were £14k, £4k and £2k.

The primary outcome measure in the key clinical trial of all-cause mortality did not reach statistical significance. However, it appeared that the modelling included a survival benefit from active treatment. When this was removed the cost per QALY estimates were £21k, £4k and £3k. It would have been helpful to see the cost per QALY estimates for the sub-group of patients with FEV\(_1\) between 50% and 60% based on the trial data and assuming no survival benefit of active treatment.

A number of clinical experts raised concerns about the rate of pneumonia in the pivotal trial in patients who had received treatments containing fluticasone. While resource use and costs associated with adverse events were collected in the trial, utility decrements for adverse events may not have been fully accounted for in the analysis. It would therefore have been helpful to see cost per QALY estimates which include quality of life decrements for pneumonia.

Due to the issues outlined above, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: The British Lung Foundation

Additional information: guidelines and protocols

NICE published a clinical guideline on the management of COPD in adults in 2004. It recommends that long-acting bronchodilators be used in patients who remain symptomatic despite treatment with short-acting bronchodilators because these drugs appear to have additional benefits over combinations of short-acting drugs. Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year.
It goes on to state that inhaled corticosteroids should be prescribed for patients with an FEV\textsubscript{1} \(\leq 50\%\) predicted, who are having two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period. If patients remain symptomatic on monotherapy, treatment should be intensified by combining therapies from different drug classes. Effective combinations include a long-acting beta2-agonist and inhaled corticosteroid. Combination treatment should be discontinued if there is no benefit after 4 weeks.

**Additional information: previous SMC advice**

After review of a full submission, on 10th May 2004, SMC advised that budesonide/formoterol inhaler (Symbicort Turbohaler®) is accepted for use within NHS Scotland for the symptomatic treatment of patients with severe COPD (FEV\textsubscript{1} <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators. It is the second of two long-acting beta2-agonist/corticosteroid combination inhaler preparations considered by SMC and licensed for the symptomatic treatment of patients with severe chronic obstructive pulmonary disease (COPD). The individual components have been available for many years and the combination product offers ease of administration and additional convenience. The combination appears to improve lung function to a greater extent than either of the individual constituents given alone. Comparative data with other combination products are limited at the present time.

After review of a full submission, on 8th December 2003, SMC advised that salmeterol/fluticasone (Seretide Accuhaler®) is accepted for use within NHS Scotland for the treatment of patients with severe chronic obstructive pulmonary disease. It is the first of two long-acting beta2-agonist/corticosteroid combination inhaler preparations considered by SMC and licensed for the symptomatic treatment of patients with severe chronic obstructive pulmonary disease (COPD). The individual components have been available for many years and the combination product offers ease of administration and additional convenience. The combination appears to improve lung function to a greater extent than either of the individual constituents given alone. Comparative data with other combination products are limited at the present time.

After review of an abbreviated submission, on 9th February 2007, issued October 2007, SMC advised that formoterol 12 micrograms metered dose inhaler (Atimos® Modulite®) is accepted for use in NHS Scotland for the relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease (COPD). It should be used in patients for whom formoterol is an appropriate choice of long-acting beta-agonist and for whom a metered dose inhaler is an appropriate delivery device.

After review of, a full submission, on 6th December 2002, SMC advised that tiotropium was recommended for general use within NHS Scotland for the maintenance treatment of chronic obstructive pulmonary disease (COPD). In clinical trials, tiotropium demonstrated superior efficacy to ipratropium and salmeterol in improving lung function (FEV1). Generally, it has greater efficacy than ipratropium, and similar efficacy to salmeterol in improving dyspnoea, the use of rescue medication, the frequency of COPD exacerbations and hospitalisation due to exacerbations.
Additional information: comparators

The only other long-acting beta2-agonist/corticosteroid combination inhaler licensed for the treatment of COPD is not licensed for the 50% to <60% FEV₁ patient population. Other treatments used in COPD include long-acting beta2-agonists, corticosteroids, (although none are licensed for use on their own in COPD), and the long-acting anticholinergic drug, tiotropium.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per year (£)</th>
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</thead>
<tbody>
<tr>
<td>Salmeterol/fluticasone</td>
<td>One inhalation twice daily</td>
<td>496</td>
</tr>
<tr>
<td>50/500 micrograms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide/formoterol*</td>
<td>One inhalation twice daily</td>
<td>461</td>
</tr>
<tr>
<td>400/12 micrograms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium</td>
<td>One inhalation daily</td>
<td>421</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>One inhalation twice daily</td>
<td>355</td>
</tr>
<tr>
<td>Formoterol</td>
<td>One inhalation once or twice daily</td>
<td>75-150</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 20.11.07.
* not licensed for use in 50 to < 60% FEV₁ patient population.

Additional information: budget impact

Based on 8,054 patients treated in year 1 rising to 9,419 in year 5, the manufacturer estimated direct drug costs of £3.9m in year 1 and £4.4m in year 5. The net drug budget impact was estimated at £49k in year 1 rising to £178k in year 5. Clinical experts suggest that the net budget impact may have been underestimated.
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 11 January 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

* Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/](http://www.scottishmedicines.org.uk/)

The undernoted references were supplied with the submission.
