

## Re-Submission

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

**No. (450/08)**

05 December 2008

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 resubmission

**salmeterol/fluticasone 50/500 micrograms 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 (FEV<sub>1</sub>) 50% to <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

While there were improvements in lung function tests and reductions in moderate exacerbations with the salmeterol/fluticasone combination compared to placebo and to salmeterol alone, there were no significant differences in mortality rates 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 in one second (FEV<sub>1</sub>) <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 beta<sub>2</sub>-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 resubmission 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, (FEV<sub>1</sub>) 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 FEV<sub>1</sub> <60% predicted, pre-bronchodilator FEV<sub>1</sub> to forced vital capacity (FVC) ratio ≤ 0.70, and with an increase of <10% predicted FEV<sub>1</sub> 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; 15.2% (231/1524), 13.5% (205/1521), 16.0% (246/1534) and 12.6% (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 interval (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 FEV<sub>1</sub> compared with all other treatments. Health status assessed in 81% (4951/6112) patients using the disease specific St George's Respiratory Questionnaire (SGRQ) showed no clinically significant differences among treatment groups. Health status was also assessed in approximately 70% of patients using the Euro-QoL questionnaire (EQ5D), a self-administered, generic scale ranging from 0=death and 1=perfect health. There was a small but significant adjusted mean difference between salmeterol/fluticasone and placebo, in the overall population but not in the 50 - 60% FEV<sub>1</sub> subgroup.

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

A post-hoc analysis of the above study, including 5,343 of the original 6,112 patients, found that the adjusted average rate of post-bronchodilator FEV<sub>1</sub> decline from week 24 onwards was 55ml/year in the placebo group, 42ml/year in both the fluticasone alone and salmeterol alone groups and 39ml/year in the combination group; corresponding to a reduction of 16 ml/year (95% CI: 7.7 to 25) with salmeterol/fluticasone versus placebo and 13 ml (95% CI: 4.3 to 22) versus placebo for both fluticasone and salmeterol alone.

Post-hoc analysis performed on the FEV<sub>1</sub> 50-<60% predicted subgroup comprising 26% (1601/6112) of total trial patients showed no significant difference between the combination and placebo groups in all-cause mortality. The hazard ratio in the 50% to <60% predicted subgroup was 0.78 (95% CI: 0.50 to 1.21).

Another randomised, double-blind, placebo-controlled trial recruited patients with a history of  $\geq 10$  pack-years of smoking, pre-bronchodilator FEV<sub>1</sub> of 25-70% predicted, pre-bronchodilator FEV<sub>1</sub> to FVC ratio  $\leq 0.70$ , increase of <10% of predicted FEV<sub>1</sub> on inhalation of 400micrograms 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 1,465 and they were treated for a period of one year. During a 2-week run-in, existing corticosteroids and long-acting beta<sub>2</sub>-agonists were discontinued. Other COPD treatments were allowed.

The primary outcome measure of pre-treatment FEV<sub>1</sub> was significantly increased by all active treatments compared with placebo. At the end of the trial, pretreatment FEV<sub>1</sub> 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.

A Cochrane review of combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for COPD analysed the use of inhaled salmeterol/fluticasone versus placebo. When the number of deaths in each treatment group of the pivotal trial was analysed by odds ratio (OR) and combined with data from four other studies, there was a significant reduction in the mortality risk in favour of salmeterol/fluticasone: OR 0.79 (95% CI: 0.65 to 0.98, n=4829). Another Cochrane review of combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists alone for COPD found no significant difference in mortality between treatments.

The effects on mortality of nine treatments for COPD were examined in a mixed treatment meta-analysis that has not yet been published. Data were analysed from 38 randomised controlled trials, including nine unpublished trials from the submitting company, providing a total of 30,916 patients. Treatment duration ranged from 12 to 183 weeks. The minimum number of participants per treatment arm was 46. The base case analysis (random effects) indicated that salmeterol/fluticasone had the lowest hazard ratio relative to placebo, HR 0.60 (95% CI: 0.38 to 0.85) compared with all other treatments.

## **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. Hazard ratio for combination treatment versus placebo: HR 1.64 (95% CI: 1.33 to 2.01). Despite the increase in adverse events labelled as pneumonia compared to the control group, there was no increase in pneumonia deaths for the combination, as adjudicated by the independent Clinical Endpoints Committee.

Adverse events that led to premature study drug discontinuation occurred in 18% (272/1546) patients in the combination treatment group, compared with 23% (356/1552) in the fluticasone, 20% (315/1542) in the salmeterol and 24% (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.

Cochrane reviewers found a significant increase in pneumonia with salmeterol/fluticasone in one inhaler in comparison with placebo, OR 1.80 (95% CI: 1.48 to 2.18) and in comparison with long-acting beta-agonist, OR 1.58 (95% CI: 1.32 to 1.88).

## 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. In the pivotal trial combined salmeterol/fluticasone did not significantly alter mortality rates compared with salmeterol alone.

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<sub>1</sub> status was not sufficiently powered to detect changes in any outcomes between treatment groups.

A Cochrane review found that salmeterol/fluticasone significantly reduced mortality risk compared with placebo.

The mixed treatment meta-analysis presented has yet to be published and was funded by the submitting company. There are a number of limitations associated with this analysis including a lack of evidence on the level of heterogeneity between trials which, if large, may produce bias; the inclusion of unpublished data from the manufacturer only, but not from other pharmaceutical companies; the inclusion of short trials which may lead to survival bias. The analysis was based on survival data corresponding only to the on-treatment period. An analysis based on longer-term follow-up data may produce different results.

Although combination treatment with salmeterol/fluticasone may slow the rate of decline of FEV<sub>1</sub> compared with placebo, the post-hoc analysis also found a significant improvement versus placebo for each drug given alone.

An important safety finding in the pivotal trial was the excess of patients who developed pneumonia among those receiving study medications containing fluticasone. This is supported by the findings of the two Cochrane reviews.

It is not clear from the evidence submitted that COPD patients with FEV<sub>1</sub> in the range 50 to <60% would benefit from combination treatment with inhaled long-acting beta<sub>2</sub>-agonists and corticosteroids compared to the use of long-acting beta<sub>2</sub>-agonists alone.

## Summary of comparative health economic evidence

The manufacturer presented a cost utility analysis comparing treatment with salmeterol/fluticasone with placebo, salmeterol, and fluticasone, for patients with COPD and an FEV<sub>1</sub> <60% predicted. A trial-based analysis was carried out based on the pivotal clinical trial and in order to adjust for missing data regression models were used to estimate survival, utilities, study drug costs and other costs. Based on the adjusted data the manufacturer estimated incremental cost-effectiveness ratios (ICERs) of £13k, £9k and £3k for the comparisons with placebo, salmeterol, and fluticasone respectively. During the review of the first submission, the sub-group of patients with FEV<sub>1</sub> between 50% and 60% was considered by SMC to be the most relevant subgroup as at this time salmeterol/fluticasone was already licensed for use in patients with FEV<sub>1</sub> <50%. Based on this subgroup, the manufacturer estimated ICERs of £15k, £8k and £3k for the comparisons with placebo, salmeterol and fluticasone respectively.

One of the problems identified with the original submission was the lack of transparency surrounding the models. The resubmission has gone some way to addressing this with more detailed and clearer explanations of the methods used. Additional sensitivity analyses were also provided using the unadjusted trial data and this provided further reassurance.

In the original submission some SMC clinical experts highlighted the increased incidence of pneumonia in patients who had received fluticasone. Although EQ-5D was collected in the clinical trial, utility decrements due to adverse events may not have been fully accounted for as EQ-5D was only administered every 6 months. Additional sensitivity analysis was provided and demonstrated that including additional utility decrements associated with pneumonia and exacerbations did not have a significant impact on the results.

The main concern with the analysis was the manufacturer's estimates of the cost per QALY cited above which were based on a difference in all-cause mortality. This was the primary outcome measure in the key clinical trial but the difference did not reach statistical significance. Based on the subgroup analysis, when the survival advantage was removed the cost per QALY estimates increased significantly to £54k, dominated and £3m for the comparisons with placebo, salmeterol, and fluticasone respectively. It should also be noted that salmeterol is probably the most appropriate comparator in this patient group and the addition of fluticasone did not reduce mortality rates compared with salmeterol alone, albeit the trial was not powered to detect this difference.

Overall, while some of the problems identified in the original review have been addressed, there is still a concern about the inclusion of the non-significant survival advantage and the resultant high cost per QALY estimates when this was removed. As a result, the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## **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<sub>1</sub> ≤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 beta<sub>2</sub>-agonist and inhaled corticosteroid. Combination treatment should be discontinued if there is no benefit after 4 weeks.

## **Additional information: previous SMC advice**

Following a full submission, Scottish Medicines Consortium (SMC) issued advice in March 2008: salmeterol/fluticasone 50/500 microgram inhaler (Seretide 500 Accuhaler<sup>®</sup>) 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 (FEV<sub>1</sub>) 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.

Following a full submission, Scottish Medicines Consortium (SMC) issued advice in December 2003: salmeterol/fluticasone (Seretide Accuhaler<sup>®</sup>) 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 b<sub>2</sub>-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.

Following a full submission, Scottish Medicines Consortium (SMC) issued advice in December 2002: tiotropium bromide (Spiriva<sup>®</sup>) 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 (FEV<sub>1</sub>). 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.

Following an abbreviated submission, Scottish Medicines Consortium (SMC) issued advice in November 2007: tiotropium respimat inhaler (Spiriva Respimat<sup>®</sup>) is accepted for restricted use within NHS Scotland as maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease. It may be used for patients in whom tiotropium is an appropriate choice of maintenance bronchodilator treatment but it is

restricted to patients who have poor manual dexterity and therefore have difficulty using the Handihaler device.

Following a full submission, Scottish Medicines Consortium (SMC) issued advice in May 2004: budesonide/formoterol inhaler (Symbicort Turbohaler®) is accepted for use within NHS Scotland for the symptomatic treatment of patients with severe COPD (FEV<sub>1</sub> <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 beta<sub>2</sub>-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.

Following an abbreviated submission, Scottish Medicines Consortium (SMC) issued advice in October 2007 (Detailed Advice Document dated 9<sup>th</sup> February 2007) 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.

### **Additional information: comparators**

The only other long-acting beta<sub>2</sub>-agonist/corticosteroid combination inhaler licensed for the treatment of COPD is not licensed for the 50% to <60% FEV<sub>1</sub> patient population. Other treatments used in COPD include long-acting beta<sub>2</sub>-agonists, corticosteroids, (although none are licensed for use on their own in COPD), and the long-acting anticholinergic drug, tiotropium.

### **Cost of relevant comparators**

<b>Drug</b>	<b>Dose regimen</b>	<b>Cost per year (£)</b>
<b>salmeterol/fluticasone 50/500 micrograms</b>	<b>One inhalation twice daily</b>	<b>496</b>
budesonide/formoterol* 400/12 micrograms	One inhalation twice daily	461
tiotropium 2.5 microgram solution for inhalation	Two inhalations daily	456
tiotropium 18 microgram capsules for inhalation	One inhalation daily	421**
salmeterol 50 micrograms	One inhalation twice daily	355
formoterol 12 micrograms	One inhalation twice daily	150

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 02.10.08. \* Not licensed for use in 50 to <60% FEV<sub>1</sub> patient population. \*\* includes the cost of one inhaler device, £3.22



### **Additional information: budget impact**

The net drug budget impact was estimated by the manufacturer to be £49k in year 1 rising to £178k in year 5. The manufacturer estimated that an additional 163 patients would receive salmeterol/fluticasone in year 1 rising to 593 in year 5, based on a market share of 39.5% in year 1 and 44.5% in year 5. These figures were based on patients switching from alternative treatments and did not include patients with an FEV<sub>1</sub> between 50% and 60% who were already being treated with salmeterol/fluticasone.

**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 14 November 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.*

*The undernoted references were supplied with the submission.*

Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356:775-89.

Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449-56.

Nannini L, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;(4):CD003794. DOI 10.1002/14651858.CD003794

Celli B, Thomas N, Anderson JA, Ferguson GT, Jenkins C, Jones PW, et al. Effect of Pharmacotherapy on Rate of Decline of Lung Function in COPD: Results from the TORCH Study. *Am J Respir Crit Care Med* 2008; 178: 332-338