HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

27 May 2009

**SERETIDE DISKUS 500/50 micrograms/dose, inhalation powder in a single dose container**
**B/28 doses with distributor (CIP code: 354 734-8)**
**B/60 doses with distributor (CIP code: 354 735-4)**

**Applicant: GLAXOSMITHKLINE**

Fluticasone (propionate), salmeterol (xinafoate)
ATC code: R03AK06

List I

Date of the Marketing Authorisation and main variations:

- 26 June 2000: Marketing Authorisation
- 22 May 2002: Modification of the following sections: Posology, Interaction with other medicinal products, Adverse effects, Overdose, Pharmacokinetic properties
- 23 May 2003: Extension of indication to symptomatic treatment of severe COPD
- 20 December 2007: Modification of the wording of the indication in COPD

Reason for request:
Modification of the wording of the indication in COPD permitting the treatment of patients with an $FEV_1$ (measured before administration of a bronchodilator) of less than 60% of the predicted value and who have a history of repeated exacerbations and significant symptoms despite regular bronchodilator therapy.

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

Fluticasone (propionate), salmeterol (xinafoate)

## 1.2. Indication

Asthma:
"SERETIDE is indicated in the regular treatment of asthma where use of a combination product (long acting beta-2-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist."

Chronic obstructive pulmonary disease (COPD):

- Previous wording:

"SERETIDE is indicated for the symptomatic treatment of patients with severe COPD ($FEV_1$ <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy."

- New wording:

**"Symptomatic treatment of COPD in patients with an $FEV_1$ (measured before administration of a bronchodilator) of less than 60% of the predicted value, and with a history of repeated exacerbations and significant symptoms despite regular bronchodilator therapy."**

## 1.3. Dosage

Adults: 1 inhalation twice daily (see SPC for details).

# 2 SIMILAR MEDICINAL PRODUCTS

## 2.1. ATC Classification (2009)

| | | |
|---|---|---|
| R | : | Respiratory system |
| R03 | : | Drugs for obstructive airway diseases |
| R03A | : | Adrenergics, inhalants |
| R03AK | : | Adrenergics and other drugs for obstructive airway diseases |
| R03AK06 | : | Salmeterol and other drugs for obstructive airway diseases |

## 2.2. Medicines in the same therapeutic category

2.2.1. Medicines in the same therapeutic category which are strictly comparable

Medicinal products combining a long-acting ß$_2$-adrenergic agonist bronchodilator with a corticosteroid, indicated in severe COPD:

Budesonide/formoterol combination:
SYMBICORT TURBUHALER 200/6 µg/dose and 400/12 µg/dose.

2.2.2. Medicines in the same therapeutic category which are not strictly comparable

Not applicable.

## 2.3. Medicines with a similar therapeutic aim

Inhaled long-acting bronchodilators indicated in the regular symptomatic treatment of COPD:

- Formoterol: ATIMOS 12 µg/dose
  FORMOAIR 12 µg/dose
  FORADIL 12 µg
  OXIS TURBUHALER 12 µg/dose
- Salmeterol : SEREVENT 25 and 50 µg/dose
  SEREVENT DISKUS 50 µg/dose
  SISEROL 25 and 50 µg/dose
  SISEROL DISKUS 50 µg/dose
- Tiotropium: SPIRIVA

ATROVENT (ipratropium), short-acting inhaled anticholinergic bronchodilator, can be used as a regular symptomatic treatment of COPD.

# 3 ANALYSIS OF AVAILABLE DATA

## 3.1. Efficacy

The modification of the wording of the indication for SERETIDE DISKUS 500/50 µg/dose in COPD is based on the TORCH study.

This randomised, double-blind comparative study included 4 treatment groups: fluticasone/salmeterol combination therapy, salmeterol, fluticasone and placebo. The main objective of this study was to evaluate, after 3 years of treatment, the effect of SERETIDE DISKUS 500/50 µg/dose on mortality in approximately 6,000 patients with COPD.

Inclusion criteria:
- Age: 40-80
- COPD characterised by:
  - a pre-bronchodilator $FEV_1$ of < 60% of the predicted value, obstruction with little or no reversibility (improvement in the $FEV_1$ of < 10% of the predicted $FEV_1$, 30 min after inhalation of 400 µg salbutamol)
  - a $FEV_1$/FVC of ≤ 70% (pre-bronchodilator $FEV_1$)
- Patients who were smokers or ex-smokers (≥ 10 pack years)

- Absence of long-term oral corticosteroid therapy (> 6 weeks), long-term oxygen therapy (≥ 12 h/day), other respiratory diseases (notably asthma) or other conditions liable to cause death during the study.

Note: The history of "repeated exacerbations and significant symptoms despite regular bronchodilator therapy" has been maintained in the new validated indication although it was not an inclusion criterion of the study.

Treatments:
The patients were randomised to receive one of the 4 treatments below for a period of 3 years:
- Fluticasone/salmeterol 500/50 µg/dose: 1 inhalation twice daily
- Salmeterol 50 µg/dose: 1 inhalation twice daily
- Fluticasone 500 µg/dose: 1 inhalation twice daily
- Placebo

During the study, the patients could receive the usual COPD treatments with the exception of inhaled corticosteroids, long-acting inhaled bronchodilators (anticholinergic agents or beta-2-agonists) and long-term systemic corticosteroids (> 6 weeks).

Primary efficacy endpoint: All-cause mortality after 3 years compared with placebo, analysed using the adjusted log-rank model taking into account 2 intermediate analyses and stratification according to smoking status.

Calculation of sample size: The number of patients to be included in the study is based on the hypothesis of a percentage of deaths after 3 years of 17% in the placebo group and a reduction of 4.3% in this percentage with fluticasone/salmeterol 500/50 µg/dose combination therapy, or a relative risk compared with placebo of 0.728, with a two-sided significance level of 0.05 and a study power of 90%. It was thus considered necessary to include 1,510 patients per group, or a total of 6,040 patients.

Secondary endpoints:
- Incidence of moderate (deterioration in symptoms requiring treatment with systemic corticosteroids and/or antibiotics) and severe (requiring hospitalisation) exacerbations
- Quality of life evaluated using the SGRQ (Saint George Respiratory Questionnaire; a change of -4 points is considered clinically relevant)

Results:
6,184 patients in total were randomised and 6,112 patients were included in the intention to treat analysis[1], comprising:
- 1,533 in the fluticasone/salmeterol group
- 1,521 in the salmeterol group
- 1,534 in the fluticasone group
- 1,524 in the placebo group

[1] ITT population: all the patients who were randomised with the exception of those patients recruited after the closure of the sites when the audit of the results or any request for information implied loss of data integrity

The patients' characteristics at inclusion were homogeneous from one group to the other. The percentage of smokers was 43% on average, with consumption of around 48 pack years. They had a pre-bronchodilator $FEV_1$ of 1.15 litre on average, 52% of the patients on average had had a moderate exacerbation and 18% a severe exacerbation during the 12 months prior to the study.

- **Primary efficacy endpoint:**

The results did not demonstrate any superiority of fluticasone/salmeterol combination therapy compared with placebo in terms of mortality after 3 years (adjusted RR vs placebo = 0.825, $CI_{95\%}$ = [0.68; 1.00], p = 0.052, see Table 1).
Furthermore, no statistically significant difference was observed either between salmeterol or fluticasone and placebo or between fluticasone/salmeterol combination therapy and salmeterol.

**Table 1:** Results in terms of all-cause mortality after 3 years

| **All-cause mortality after 3 years** | **Fluticasone/ salmeterol 500/50 µg/dose N = 1,533** | **Salmeterol 50 µg/dose N = 1,521** | **Fluticasone 500 µg/dose N = 1,534** | **Placebo N = 1,524** |
|---|---|---|---|---|
| Number of deaths (%) | 193 (12.6%) | 205 (13.5%) | 246 (16.0%) | 231 (15.2%) |
| Adjusted RR vs placebo<br>$CI_{95\%}$<br>p | 0.825<br>[0.68; 1.00]<br>0.052 | 0.879<br>[0.73; 1.06]<br>0.180 | 1.060<br>[0.89; 1.27]<br>0.525 | - |
| RR combination vs each of the components of the combination<br>$CI_{95\%}$<br>p | - | 0.932<br>[0.77; 1.13]<br>0.481 | 0.774<br>[0.64; 0.93]<br>0.007 | - |

- **Secondary endpoints:**

The frequency of moderate-to-severe exacerbations was lower in the fluticasone/salmeterol group than in the salmeterol group (0.85 compared with 0.97 exacerbation/patient/year, RR = 0.878, $CI_{95\%}$ = [0.808; 0.954], p = 0.002).
No statistically significant difference was observed between fluticasone/salmeterol combination therapy and salmeterol in terms of severe exacerbations (0.16 exacerbation/patient/year in both groups, RR = 1.022, $CI_{95\%}$ = [0.870; 1.200], NS).

The change in the average total SGRQ quality of life score over the total period of the study (results for the per protocol population) was -3.0 ± 0.35 in the fluticasone/salmeterol group and -0.8 ± 0.35 in the salmeterol group. These improvements did not achieve the threshold of clinical relevance, however (change of -4 points).

### 3.2. Adverse events

The adverse events reported during the TORCH study were those usually observed with fluticasone and salmeterol, in conformity with the information in the SPC. The higher incidence of lower respiratory tract infections, and pneumonia and bronchitis in particular, in the groups treated with fluticasone alone or in combination, compared with the placebo group, constitutes a new safety factor.

The frequency of pneumonia was 19.6% with the fluticasone/salmeterol combination, 18.3% with fluticasone, 13.3% with salmeterol and 12.3% with placebo. The risk of developing a first episode of pneumonia during the 3 years of the study was increased in the fluticasone/salmeterol group compared with placebo, with a hazard ratio of 1.64 ($CI_{95\%}$ = [1.33; 2.02], p < 0.001).

In this study, this risk of developing pneumonia, independently of treatment, was higher in elderly patients (> 65 years of age), in those with more severe COPD ($FEV_1$ of < 30% of the predicted value) and in those with a BMI of < 25 kg/$m^2$.

These results led to modification of the following sections: “Special warnings and precautions for use” and “Adverse effects”. It is specified in particular that the occurrence of pneumonia in an elderly subject with COPD at a severe stage must prompt a reevaluation of treatment with SERETIDE.

### 3.3. Conclusion

The pharmaceutical company’s request is based on the TORCH study which compared fluticasone/salmeterol 500/50 µg/dose combination therapy with fluticasone 500 µg/dose alone, salmeterol 50 µg/dose alone and placebo using an endpoint of all-cause mortality in patients with moderate-to-severe COPD ($FEV_1$ of < 60% of the predicted value) with little or no reversibility. No requirement was specified in terms of the history of exacerbations.
The results did not demonstrate any superiority of fluticasone/salmeterol combination therapy over placebo in terms of effect on all-cause mortality after 3 years (adjusted RR vs placebo = 0.825, $CI_{95\%}$ = [0.68; 1.00], p = 0.052). A favourable effect of fluticasone/salmeterol combination therapy compared with salmeterol was observed only in respect of the secondary endpoints: frequency of moderate-to-severe exacerbations (0.46 exacerbation/patient/year with combination therapy compared with 0.64 with salmeterol, RR = 0.708, $CI_{95\%}$ = [0.631; 0.793], p<0.001) and quality of life (although clinical relevance was not achieved). Fluticasone/salmeterol combination therapy was not superior to salmeterol when the severe exacerbations alone were considered, however.

In the course of this study, cases of pneumonia were observed more frequently with fluticasone/salmeterol combination therapy than with the placebo (HR = 1.64; $CI_{95\%}$ = [1.33; 2.02]; p < 0.001). Elderly subjects (> 65 years of age), patients with severe COPD ($FEV_1$ of < 30% of the predicted value) and those with a BMI of < 25 kg/$m^2$ are considered to be at greater risk of pneumonia during treatment with combined fluticasone/salmeterol.

The results of the TORCH study (absence of effect on all-cause mortality and greater frequency of pneumonia with fluticasone/salmeterol 500/50 µg/dose combination therapy) are consistent with the results of the Drummond meta-analysis (2008)[2], which did not identify any reduction in all-cause mortality and which showed an increased frequency of pneumonia in patients with COPD treated with inhaled corticosteroids compared with those treated with bronchodilators.

[2] Drummond MB et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008 Nov 26;300(20):2407-16. This meta-analysis compared inhaled corticosteroids with placebo and fixed corticosteroid/long-acting beta-2-agonistcombinations with a long-acting beta-2-agonist or tiotropium

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

COPD is debilitating, causes a marked deterioration in quality of life and can be life-threatening.

Public health benefit:

The public health burden of COPD is considerable. The subpopulation made up of patients able to benefit from treatment with SERETIDE DISKUS 500/50 µg/dose represents a significant burden.

Improving the management of COPD constitutes a public health need within the scope of an identified priority (GTNDO priorities[3]). However, for the symptomatic management of COPD, the therapeutic need is met by existing symptomatic treatments.

In view of the data from clinical trials and taking into account the available alternatives, this medicinal product is not expected to have an impact in terms of morbidity and mortality or quality of life.

As a consequence, it is not expected that the medicinal product SERETIDE DISKUS 500/50 µg/dose will benefit public health.

Because of the small effect associated with adding a high-dose inhaled corticosteroid to a long-acting bronchodilator and the risk of infection (notably pneumonia) in a vulnerable population (elderly patients, smokers, with co-morbidities), the efficacy / adverse effects ratio of this medicinal product is low.

This medicinal product is a regular symptomatic treatment for COPD in patients with a pre-bronchodilator $FEV_1$ of < 60 %, with a history of repeated exacerbations and significant symptoms despite regular bronchodilator therapy.

There are no grounds for routinely combining an inhaled corticosteroid with a long-acting bronchodilator in the treatment of COPD.

This medicinal product is a second-line therapy in cases of failure to respond to regular treatment with a long-acting bronchodilator, in a small group of patients. As a consequence, the therapeutic use of this medicinal product is very limited.

Alternatives exist.

The actual benefit of SERETIDE DISKUS 500/50 µg per dose is moderate in this indication.

### 4.2. Improvement in actual benefit (IAB)

SERETIDE DISKUS 500/50 µg/dose does not provide any improvement in actual benefit (level V) in the management of patients with COPD with a pre-bronchodilator $FEV_1$ of < 60% of the predicted value and a history of repeated exacerbations and significant symptoms despite regular bronchodilator therapy.

[3] Groupe Technique National de Définition des Objectifs (DGS-2003)

## 4.3. Therapeutic use

### 4.3.1. Treatment strategy

The diagnosis and management of patients with COPD must involve an evaluation of the stage of severity of the COPD based on an examination of the symptoms (chronic cough, dyspnoea on exertion, production of pus, exacerbations) and respiratory function tests.

No medicinal product is able to prevent the long-term progression of COPD towards chronic respiratory failure. The first measure to be implemented is reducing the risk factors, particularly smoking cessation. Exercise rehabilitation and respiratory physiotherapy help to improve symptoms, quality of life and participation in daily activities.

The pharmacological management of stable COPD (separate from exacerbations) uses a staged approach depending on the stage of severity and response to treatment. The medicines used are targeted at reducing the symptoms and decreasing the frequency and severity of the complications associated with exacerbations.

Bronchodilators, taken as required or on a regular basis, constitute the main symptomatic treatment for COPD. These are mainly beta-2-agonists and anticholinergic agents, available in an inhaled form. Theophyllines may be used if the patient has difficulty using inhaled bronchodilators or if the latter do not improve the dyspnoea sufficiently; their use is limited by their narrow therapeutic range.
Short-acting inhaled bronchodilators (beta-2-agonists or anticholinergic agents), taken as required, are recommended as first-line therapy.

Long-acting bronchodilators are recommended when regular symptomatic treatment is necessary, i.e. when the dyspnoea persists despite the use of a short-acting bronchodilator several times a day.
Two beta-2-agonists are available, formoterol and salmeterol. They have demonstrated a benefit over placebo.
Tiotropium (long-acting anticholinergic agent) has demonstrated a benefit over placebo and ipratropium (short-acting anticholinergic agent) but, compared with long-acting beta-2-agonists, the differences observed have not been clinically relevant.
These three medicinal products are first-line therapies in the regular symptomatic treatment of COPD.

Inhaled corticosteroids can be used only in combination with a long-acting bronchodilator in patients with severe COPD with an $FEV_1$ of < 50% of the predicted value and repeated exacerbations. They have not demonstrated any effect on all-cause mortality and increase the risk of lower respiratory tract infections, particularly pneumonia, in patients who are already at risk because of the severity of their condition, their age and co-morbidities.

Treatment with a long-acting bronchodilator or a long-acting bronchodilator plus an inhaled corticosteroid is purely symptomatic. It should be continued only if a beneficial effect is observed on the symptoms.
Systemic corticosteroids are not recommended.

Oxygen therapy is limited to patients with diurnal hypoxaemia ($PaO_2 \leq 55$ mm Hg), not during an acute episode and despite optimal treatment.

4.3.2. Use of the medicinal product

The new indication for salmeterol/fluticasone combination therapy permits the treatment of patients with an $FEV_1$ of < 60% of the predicted value, a history of repeated exacerbations and significant symptoms despite regular bronchodilator therapy. However, according to the GOLD recommendations updated in November 2008[4] (the 2003 SPLF recommendations are under review), corticosteroid/long-acting bronchodilator combinations are still limited to patients with severe COPD and an $FEV_1$ of < 50% of the predicted value and repeated exacerbations. Respiratory function tests must be performed to confirm the stage of severity of the COPD before treatment with SERETIDE DISKUS 500/50 µg/dose.

It should be noted that no dose study has been conducted and that this medicinal product, consisting of an inhaled high-dose corticosteroid (1,000 µg/day fluticasone, equivalent to 2,000 µg/day beclomethasone), administered on a long-term basis, is intended for patients who, vulnerable as a result of both their age and the severity of their condition, will be sensitive to the adverse effects associated with inhaled corticosteroids, particularly pneumonia.

## 4.4. Target population

The target population for SERETIDE DISKUS 500/50 µg/dose in the new indication corresponds to patients with COPD who have an $FEV_1$ of < 60% of the predicted value and who have a history of repeated exacerbations and symptoms despite regular bronchodilator therapy.

According to the French epidemiological data[5, 6, 7, 8, 9] available, around 3.5 million people are thought to suffer from chronic bronchitis progressing to COPD in a third of cases, i.e. around 1,150,000 patients.

According to the European epidemiological data[10, 11] available, severe forms ($FEV_1$ <50 % of the predicted value) represent around 25% of patients with COPD, or 288,000 patients. According to these same data, moderate forms (50% ≤ $FEV_1$ < 70% of the predicted value) represent around 40% of COPD cases. Assuming approximately equal distribution between the forms with an $FEV_1$ of 50-59% of the predicted value and those with an $FEV_1$ of 60-69% of the predicted value, the proportion of moderate forms with an $FEV_1$ of 50-59% can be estimated at around 20%, or 230,000. In summary, the population of patients with COPD characterised by an $FEV_1$ of < 60% of the predicted value can be estimated at around 518,000.

There are no epidemiological data which enable an estimate to be made of the population of patients with persistent symptoms and repeated exacerbations despite regular bronchodilator therapy. According to the data from the previous clinical studies, it can be considered that around 30% of patients at this stage of severity have at least 2 exacerbations/year, or 155,000.

Insofar as the product is already indicated in asthma, it is advisable to exclude from the target population the subgroup of patients with associated asthma. According to the data available[2, 12], around 20% of patients with COPD also have asthma. On this basis, the target

[4] http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003
[5] Recommandations of the SPLF (1997)
[6] Huchon et al. The European Respiratory Society Annual Congress (2001)
[7] Huchon. La presse médicale (2001)
[8] Huchon et al. European Respiratory Journal (2002)
[9] Neurkich et Perdrizet. Revue des Maladies Respiratoires (1998)
[10] Pena et al. IBERPOC multicenter epidemiological study. CHEST 2000
[11] Zielinski J et al. Pneumolol. Alergol. Pol. (2000)
[12] Lundbäck et al. Eur. J. Epidemiol (1993)

population for SERETIDE DISKUS 500/50 µg/dose in the new indication, supplementary to the population already treated for asthma, should not exceed 125,000 patients.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services in the new indication and at the dosages in the Marketing Authorisation.

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4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%.