# Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

# Seretide Diskus
# Salmeterol xinafoate, fluticasone propionate

# SE/W/0005/pdWS/004
# Marketing Authorisation Holder: GlaxoSmithKline

| | |
|---|---|
| **Rapporteur:** | Sweden |
| **Finalisation procedure (day 90):** | 12 April 2016 |

**ADMINISTRATIVE INFORMATION**

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|---|---|
| Invented name of the medicinal product: | Seretide Diskus |
| INN (or common name) of the active substance(s): | Salmeterol xinafoate, fluticasone propionate |
| MAH: | GlaxoSmithKline |
| Currently approved Indication(s) | **Asthma**<br>Seretide is indicated in the regular treatment of asthma where use of a combination product (longacting beta-2-agonist and inhaled corticosteroid) is appropriate:<br>- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist<br>or<br>- patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.<br>Note: Seretide 50 microgram/100 microgram strength is not appropriate in adults and children with severe asthma.<br>**Chronic Obstructive Pulmonary Disease (COPD)**<br>Seretide is indicated for the symptomatic treatment of patients with COPD, with a FEV1 <60%<br>predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. |
| Pharmaco-therapeutic group (ATC Code): | R03AK06 |
| Pharmaceutical form(s) and strength(s): | Dose inhalation powder, pre-dispensed. |

# I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

# II. RECOMMENDATION

The data presented from study ASR115645 does not change benefit/risk for the paediatric population. No further action required.

# III. INTRODUCTION

On 3 December 2015, the MAH submitted a completed paediatric study for Seretide Diskus, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The MAH stated that the submitted paediatric study does not influence the benefit/risk for Seretide Diskus and that there is no consequential regulatory action.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the study

The product used is Seretide Diskus containing 50 mcg salmeterol xinafoate and 250 mcg fluticasone propionate. It is the mid strength (two other strengths with lower and higher content of fluticasone propionate respectively is marketed) approved for use in adults and adolescents from 12 years of age indicated for asthma.

## IV.2 Clinical aspects

### 1. Introduction

The MAH submitted a final report for:

- ASR115645: A randomised, multi-centre, double-blind, double-dummy, two way cross-over, twelve weeks non-inferiority study to evaluate the efficacy, safety, and tolerability of combination dry powder of fluticasone propionate and salmeterol 250/50mcg twice daily delivered through a capsule-based inhaler and a multi-dose inhaler in adults and adolescents with asthma.

### 2. Clinical study

**ASR115645: A randomised, multi-centre, double-blind, double-dummy, two way cross-over, twelve weeks non-inferiority study to evaluate the efficacy, safety, and tolerability of combination dry powder of fluticasone propionate and salmeterol 250/50mcg twice daily delivered through a capsule-based inhaler and a multi-dose inhaler in adults and adolescents with asthma.**

## ➢ Description

This study was a Phase III study performed in compliance with GCP. The study was sponsored by GlaxoSmithKline (GSK) and conducted at 13 centres in two countries: Russia (six centres) and Ukraine (seven centres). Seretide Diskus was used as the reference product in this study.

## ➢ Methods

- Objective(s)

The primary objective of this study was to establish the non-inferiority of the efficacy of Seretide Diskus and a similar product (fluticasone propionate/salmeterol 250/50 mcg) where the dose is delivered with a unit-dose capsule inhaler (Rotahaler) in adults and adolescents with asthma.

The secondary objectives included the evaluation of the safety, tolerability, and pharmacodynamics of the two inhalers and their effect on the asthma control of these subjects.

- Study design

This was a multi-centre, randomised, double-blind, double-dummy, two-way cross-over, 12-week non-inferiority study. The study consisted of six phases: Pre-screening, screening/Run-in (3 weeks), treatment period 1 (12 weeks), washout (minimum 3 weeks), treatment period 2 (12 weeks), and follow-up (1 week).

- Study population /Sample size

This study recruited male and female (non-pregnant and non-lactating) subjects ≥12 and ≤80 years with a diagnosis of asthma who at Visit 1 had a best pre-bronchodilator FEV1 between ≥ 40% and ≤ 85% of predicted normal value and demonstrated ≥ 12% and ≥ 200 mL reversibility of FEV1 within 10 to 40 minutes after two to four inhalations of salbutamol inhalation aerosol or equivalent nebulised treatment with salbutamol solution. Subjects must have been using an ICS with or without LABA for at least 8 weeks and on a stable dose for at least 4 weeks before Visit 1.

- Treatments

Regimen A: One inhalation from placebo Diskus followed by one inhalation from a single administration of Rotacap, administered each morning and evening
or
Regimen B: One inhalation Seretide Diskus followed by one inhalation placebo Rotahaler each morning and evening

- Outcomes/endpoints

The primary efficacy endpoint was the change from baseline in trough morning forced expiratory volume in 1 second (FEV1) at Day 85 of each treatment period. The secondary efficacy endpoints were serial FEV1 results on Day 1 and Day 85 (summarised as area under the curve, $AUC_{0 \text{ to } 12 \text{ hours}}$) and the change from baseline in each of the following: trough FEV1 at Day 28 and 56, morning peak expiratory flow rate (PEFR), rescue medication use, day- and night-time asthma symptom scores, percentage of symptom-free days, percentage of rescue-free days, and Asthma Control Test (ACT) results.

Safety and tolerability endpoints were AE monitoring; incidence of asthma exacerbations, severe asthma exacerbations, and oral candidiasis; vital sign measurements; 12-lead ECG findings; and clinical chemistry results.

Pharmacodynamic endpoints were the assessment of serial serum cortisol AUC (0 to 12 hours) and minimum concentration (Cmin) (1, 2, 6, and 12 hours after the last morning dose on Day 85) in a subset of subjects and the change from Baseline in mean vital sign measurements (heart rate, systolic blood pressure, and diastolic blood pressure).

- Statistical Methods

The study was designed and powered to show non-inferiority between the two treatments for the change from Baseline in morning trough FEV1 at Day 85. Non-inferiority was assessed by examination of the lower limit of the CI (0.025, one-sided significance level) against the non-inferiority margin of -125 ml. The primary comparison was for the ITT Population.

## ➢ Results

- Demographics and baseline characteristics

A total of 84 subjects were randomly assigned to study treatment and 78 completed both periods. The majority of subjects were middle-aged (mean age 52.5 years) and female (56%). Five subjects (6%) were adolescents (range: 11 to 16 years old). All five adolescent subjects were enrolled by the same investigator at the same site in the Ukraine.

The mean baseline morning trough FEV1 values were similar between the fluticasone propionate/salmeterol (FSC) ROTAHALER and FSC DISKUS treatment groups.

**Table 1** Summary of Morning Trough FEV1 (L) at Baseline

| | FSC ROTAHALER N=82 | FSC DISKUS N=82 |
|---|---|---|
| n | 82 | 80 |
| Mean (SD) | 1.936 (0.6582) | 2.021 (0.6945) |
| Median | 1.780 | 1.920 |
| Minimum, maximum | 0.88, 4.11 | 0.70, 4.67 |

Source: Table 6.1.

$FEV_1$ = forced expiratory volume in 1 second; FSC = fluticasone propionate/salmeterol combination; ITT = intent to treat; SD = standard deviation.

- Efficacy results

**Table 2** Analysis of Change From Baseline in Morning Trough FEV1 (L) at Day 28, Day 56, and Day 85

| | FSC ROTAHALER N=82 | FSC DISKUS N=82 |
|---|---|---|
| **Day 28** | | |
| Model-adjusted change from Baseline[1] | | |
| n | 81 | 80 |
| LS mean | 0.245 | 0.238 |
| Standard error | 0.0402 | 0.0405 |
| 95% CI | (0.166, 0.325) | (0.158, 0.318) |
| Difference from FSC DISKUS[1] | | |
| Difference of LS means | 0.007 | |
| 95% CI | (-0.074, 0.088) | |
| **Day 56** | | |
| Model-adjusted change from Baseline[1] | | |
| n | 78 | 80 |
| LS mean | 0.224 | 0.202 |
| Standard error | 0.0378 | 0.0377 |
| 95% CI | (0.149, 0.299) | (0.128, 0.277) |
| Difference from FSC DISKUS[1] | | |
| Difference of LS means | 0.022 | |
| 95% CI | (-0.049, 0.092) | |
| **Day 85** | | |
| Model-adjusted change from Baseline[1] | | |
| n | 78 | 80 |
| LS mean | 0.231 | 0.203 |
| Standard error | 0.0339 | 0.0338 |
| 95% CI | (0.164, 0.298) | (0.136, 0.269) |
| Difference from FSC DISKUS[1] | | |
| Difference of LS means | 0.028 | |
| 95% CI | (-0.024, 0.080) | |

Source: Table 6.2.

CI = confidence interval; $FEV_1$ = forced expiratory volume in 1 second; FSC = fluticasone propionate/salmeterol combination; ITT = intent to treat; LS = least squares.

1. Based on mixed model for repeated measures analysis: Change from Baseline = Subject-level Baseline + Adjusted treatment period-specific Baseline + Treatment group + Treatment period + Visit + Visit*treatment + Visit*Subject-level Baseline + Visit*adjusted treatment period-specific Baseline, with subject as a random effect.

- Safety results

The incidence of subjects who experienced on-treatment AEs was lower in the FSC ROTAHALER treatment group (27%) than in the FSC DISKUS treatment group (34%). In both treatment groups, no on-treatment AEs were considered related to study treatment or led to study drug discontinuation or study withdrawal. No on-treatment SAEs and no fatal SAEs were reported for this study.

The most frequently reported on-treatment AEs were headache, hypertension, and increased blood pressure.

### 3. Discussion on clinical aspects

The MAH has presented data from a study ASR115645. Data were provided in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use as among the included subjects were 5 adolescents. Considering the low number of included paediatric patients in relation to the size of the total database and the fact that no severe or unexpected adverse events were recorded in this study it is concluded that the results does not change the benefit/risk balance for the product.

## V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The data presented from study ASR115645 does not change benefit/risk for the paediatric population.

- **Recommendation**

No further action required