

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

**Seretide Evohaler/Viani Evohaler, Seretide Diskus/Viani
Diskus
(Salmeterol xinafoate/fluticasone propionate)**

SE/W/005/pdWS/001

Marketing Authorisation Holder: GlaxoSmithKline

Rapporteur:	Sweden
Start of the procedure (day 0):	4 April 2009
Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):	17 June 2009
Deadline for CMS's comments (day 85):	2 July 2009
Date of revised report (Day 89)	6 July 2009
Date re-start procedure (day 90):	1 December 2009
Deadline for CMS's comments (day 115):	6 January 2009
Finalisation procedure (day 120):	12 January 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Seretide Diskus/Viani Diskus Seretide Evohaler
INN (or common name) of the active substance(s):	Salmeterol xinafoate+Fluticasone propionate
MAH:	GlaxoSmithKline
Currently approved Indication(s)	<p><u>Seretide Diskus/Viani Diskus:</u> <i>Asthma</i> Salmeterol/Fluticasone propionate is indicated in the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate:</p> <ul style="list-style-type: none"> - Patients not adequately controlled with inhaled corticosteroids and “as needed” short-acting beta-2-agonist. <p>or</p> <ul style="list-style-type: none"> - Patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist <p>Note: Salmeterol/Fluticasone propionate 50 microgram /100 microgram strength is not appropriate in adults and children with severe asthma.</p> <p><i>Chronic Obstructive Pulmonary Disease (COPD)</i> Salmeterol/Fluticasone propionate is indicated for the symptomatic treatment of patients with COPD with a FEV1 <60 % predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.</p> <p><u>Seretide Evohaler/Viani Evohaler:</u> <i>Asthma</i> Salmeterol/Fluticasone propionate is indicated in the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate:</p> <ul style="list-style-type: none"> - Patients not adequately controlled with inhaled corticosteroids and “as needed” short-acting beta-2-agonist. <p>or</p> <ul style="list-style-type: none"> - Patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist
Pharmaco-therapeutic group (ATC Code):	R03AK06
Pharmaceutical form(s) and strength(s):	<u>Seretide Diskus/Viani Diskus:</u> Powder for inhalation, 50 µg/100 µg, 50 µg/250 µg, 50

	<p>µg/500 µg</p> <p><u>Seretide Evohaler/Viani Evohaler:</u></p> <p>Pressurised suspension for inhalation, 25 µg/50 µg, 25 µg/125 µg, 25 µg/250 µg</p>
<p>Rapporteur's contact person:</p> <p>Name of the Assessor:</p>	<p>Name: Eva Agurell Tel: +46 18 174971 Email: eva.agurell@mpa.se</p> <p>Clinical Pharmacokinetics: Name: Eva Gil Berglund Tel: +46 18 4731 Email: Eva.Gil_Berglund@mpa.se</p> <p>Efficacy and safety: Name: Eva Agurell Tel: +46 18 174971 Email: eva.agurell@mpa.se</p>

I. INTRODUCTION

The MAH submitted 11 completed paediatric studies in accordance with Article 46 of the Regulation (EC) No 1901/2006.

The focus on this assessment has been to review the submitted studies to determine if new results and findings have emerged that would suggest any change in the already approved paediatric indication and posology. The level of assessment also depended on the population included in the studies. Emphases have been to assess the new safety data.

II. SCIENTIFIC DISCUSSION

Seretide is a combination product containing, salmeterol xinafoate and fluticasone propionate. The active substances are well-known and belong to the Pharmacotherapeutic Group: Adrenergics and other anti-asthmatics. Seretide is provided as a pressurised metered dose (MDI) inhaler, i.e. Seretide Evohaler, or a dry powder inhalator (DPI), i.e. Seretide Diskus or Viani Diskus. The delivered single doses are 25 µg/50 µg per inhalation for Seretide Evohaler and 50 µg/100 µg per inhalation for Seretide Diskus or Viani Diskus. Seretide Diskus was approved in Sweden on the 7th of September 1998.

Seretide Evohaler and Seretide Diskus/Viani Diskus are approved in all EU countries either through mutual recognition (MR) procedure(s) (SE/H/169/01-03, SE/H/170/01-03, UK/H/392/01-03, UK/H/398/01-03) or by national procedures. In the MR procedure(s), the following CMSs have been involved AT, BE, DE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NL and PT with SE and/or UK as RMS. During the first MRP, Seretide Diskus was mutually approved on the 22nd of December 1998 (Day 90). The paediatric indication was already included in the original approval. The following EU countries BG, CZ, CY, EE, HU, LT, LV, MT, NO, PL, RO, SI and SK have approved Seretide nationally.

The approved MR indication for paediatrics is:

Asthma

Salmeterol/Fluticasone propionate 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” short-acting beta-2-agonist

or

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

Note: Seretide 50 microgram/100 microgram strength is not appropriate in adults and children with severe asthma. (only DPI)

The approved MR posology for paediatrics is:

Recommended dosage in asthma

Adults and adolescents 12 years and older

For the MDI, i.e. for Seretide/Viani Evohaler

-2 inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily

daily -2 inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice

daily -2 inhalations of 25 micrograms salmeterol and 250 micrograms fluticasone propionate twice

or

For the DPI, i.e. for Seretide Diskus/Viani Diskus

daily -1 inhalations of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice

-1 inhalations of 50 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily

-1 inhalations of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily

A short term trial of Salmeterol/Fluticasone propionate may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is two inhalations (25 micrograms salmeterol and 50 micrograms fluticasone propionate) twice daily (MDI) *or one inhalations (50 micrograms salmeterol and 100 micrograms fluticasone propionate) twice daily (DPI)*. Once control of asthma is attained treatment should be reviewed and consideration given as to whether the treatment can be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

Clear benefit has not been shown in comparison with inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general, inhaled corticosteroids remain the first-line treatment in most patients. Salmeterol/Fluticasone propionate is not intended for the initial management of mild asthma. Salmeterol/Fluticasone propionate 25/50 microgram strength (MDI) *or Salmeterol/Fluticasone propionate 50 microgram/100 microgram strength (DPI)* is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed combination can be used in patients with severe asthma.

Children 4 years and older

Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily. (MDI)

or

One inhalations of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily. (DPI).

The maximum licensed dose of fluticasone propionate delivered by Salmeterol/Fluticasone propionate *inhaler/Diskus* in children is 100 micrograms twice daily when administered via Salmeterol / Fluticasone propionate inhaler.

There are no data available for use of Salmeterol/Fluticasone propionate children aged under 4 years.

Use of a spacer device with the Salmeterol/Fluticasone propionate inhaler is recommended in patients who find it difficult to synchronise aerosol actuation with inspiration of breath. Either the Volumatic or AeroChamber Plus spacer device can be used (depending on National Guidance). Limited data are available that demonstrate an increase in systemic exposure when the AeroChamber Plus spacer device is used compared with the Volumatic spacer device (see section 4.4). (*only MDI*).

Patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs. **Patients should continue to use the same make of spacer device as switching between spacer devices can result in changes in the dose delivered to the lungs (see section 4.4).** (*only MDI*).

Re-titration to the lowest effective dose should always follow the introduction or change of a spacer device. (*only MDI*).

II.1 Clinical aspects

The MAH submitted reports for 11 studies. A summary of the submitted studies are shown in Table 1.

Study medication, the combination product salmeterol / fluticasone propionate (SFC), was provided as a pressurised metered dose (MDI) inhaler or a dry powder inhalator (DPI). The delivered single doses for children are 25 µg/50 µg per inhalation for the MDI and 50 µg/100 µg per inhalation for the DPI.

Study PEACE (SAM103848):

Table 1. Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
PEACE (SAM103848) Multicenter, randomised, double-blind, double dummy, parallel group 12 weeks	Salmeterol/Fluticasone propionate Inhalation Powder (50/100 mcg BID) via DISKUS, DPI, (Daily dose: 100/200 mcg) or Montelukast (5mg QD) Chewable Tablets	Primary: to demonstrate the superior clinical effectiveness of Salmeterol/Fluticasone Propionate (SFC) compared with montelukast in the management of persistent asthma. Secondary: to assess the effect of each treatment Salmeterol/Fluticasone Propionate (50/100 mcg) and montelukast (5 mg)] on lung function, asthma control, Health Outcomes.	Children , male or female subjects, 6-14 years of age with a diagnosis of moderate to severe persistent asthma for at least 6 months and a FEV1 between 55% and 80% of predicted normal and ≥12% FEV1 reversibility following inhalation of salbutamol.	548 (SFC:281 Montelukast: 267) 335/213 (SFC:156/126 Montelukast: 179/88) 6-15 years (SFC:6-14 Montelukast: 6-15)

For the primary efficacy endpoint, change from baseline in morning peak flow, treatment with SFC 50/100µg bd is shown to be statistically significantly better than montelukast over the 12 weeks studied. Overall, the results of the secondary efficacy measures support the primary efficacy endpoint. Thus, the efficacy of salmeterol/fluticasone propionate DPI is further confirmed in children by this study.

The incidence of adverse events is similar in both groups and the treatments are well tolerated. No unexpected adverse events are observed in the SFC treatment group. Thus, this study confirms the well established safety profile from earlier studies. In conclusion, there is no new information leading to modifications of the Summary of Product Characteristics (SmPC).

Study SAS110099:

Table 1, cont. Overview of the submitted clinical studies (Rotadisk=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
SAS110099 Multicentre, randomised, open-label, two-period crossover study followed by an extension treatment period	<u>Crossover:</u> GW815SF (salmeterol/fluticasone propionate, 25/50 mcg, BID) HFA MDI, (Daily dose: 50/100 mcg) or Salmeterol (SLG) DPI (25 mcg BID) + Fluticasone propionate (FP) DPI (50 mcg BID) (Daily dose: 50+100)	Primary: to determine the equivalence by morning Peak Expiratory Flow (PEF), of one inhalation of GW815SF HFA MDI 25/50mcg twice daily to one inhalation of SLM DPI 25mcg twice daily plus one inhalation of FP DPI 50mcg twice daily in a crossover manner. Secondary: to determine the long-term safety of one	Children , male or female Japanese subjects, 5-14 years of age with a diagnosis of mild to moderate persistent bronchial asthma (96% of patients had a duration of ≥6 months). who have been treated with ICS (FP 100mcg/day or equivalent) for at least 4 weeks prior to the start of	<u>Crossover period:</u> 51 (SFC first:26 SLG+FP first: 25) 34/17 5-14 years <u>Extension period:</u> 50 (SFC:50)

<u>Crossover:</u> 4 weeks <u>Extension:</u> 20 weeks	mcg) <u>Extension period:</u> GW815SF HFA MDI 25/50mcg twice daily. (Daily dose: 50/100 mcg)	inhalation of GW815SF HFA MDI 25/50 mcg twice daily.	run-in period	33/17 5-14 years
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This small open study was performed to gain knowledge of the effect and safety of Seretide in Japanese children. Bioequivalence of salmeterol/fluticasone propionate is demonstrated between the salmeterol/fluticasone propionate MDI and Salmeterol xinofoate and fluticasone propionate DPI inhalers (during the 4-week crossover period) and the effect is maintained during the 20-week extension period.

Further, no unexpected adverse events occur during the long term safety period (24 weeks). In conclusion, this small study consisting of 50 Japanese children confirms the well established safety data from earlier studies. Salmeterol/fluticasone propionate is well tolerated by the patients and the adverse effects are well known. Thus, no SmPC modifications are suggested.

Study SAS110101:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
SAS110101 Multicentre, non-comparative, open-label, long-term study 24 weeks	2 inhalations of GW815SF (salmeterol /fluticasone propionate) HFA MDI 25/50mcg twice daily (Daily dose: 100/200 mcg)	<u>Primary:</u> to determine the long-term safety of two inhalations of GW815SF HFA MDI 25/50 mcg twice daily.	Children , male or female Japanese subjects, 5-14 years of age with a diagnosis of moderate to severe persistent bronchial asthma who have been treated with ICS (FP 100-200mcg/day or equivalent) for at least 4 weeks prior to the start of run-in period.	40 24/16 5-14 years

In this small open study in Japanese children, no unexpected adverse events are observed during the long term safety period (24 weeks). The well established safety profile from earlier studies is confirmed. Thus, there is no new significant information leading to modifications of the SmPC.

Study SFA106484:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
SFA106484 Multicenter, randomised, double-blind, double dummy, parallel group study 12 weeks	2 inhalations of salmeterol /fluticasone propionate) HFA MDI 25/50mcg twice daily (Daily dose: 100/200 mcg) or 2 inhalations of fluticasone propionate) HFA MDI 50mcg twice daily	<u>Primary:</u> to evaluate the safety of salmeterol/fluticasone propionate 50/100mcg HFA (SF 100/50 HFA) twice daily compared with fluticasone propionate 100mcg HFA (F 100 HFA) twice daily	Children , male or female subjects, 4-11 years of age with a diagnosis of severe persistent bronchial asthma who have been treated with ICS for at least 2 months prior to screening period.	350 (SFC: 173; FP: 177) 213/137 (SFC: 107/66); FP: 106/71) 4-11 years (SFC mean 7.7 years;

	(Daily dose: 200 mcg)			FP: mean 7.6 years) Spacer use: among 4-5 years: SFC 92% FP: 95% among 6-11 years: SFC 74% FP: 72%
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In this study 4-11 year old children was provided study medication with the MDI HFA inhalers. The AeroChamber Plus spacer was utilized by the majority of subjects, approximately 78% and 77% of the SFC group and FP group, respectively.

Efficacy is demonstrated since a statistically significantly greater increase from Baseline in FEV1 (0.23 L) is noted in the SFC 100/50 HFA group when compared with FP 100 HFA group (0.17 L). Over Weeks 1-12 PEF increases from Baseline are also higher in the SFC 100/50 HFA group than the FP 100 HFA group. However, no subanalysis was performed with respect to spacer use in the treatment group. The MAH were asked to perform a subanalysis with respect to spacer use in the SFC and FP treatment groups and further discuss the results in relation to the questions raised regarding the possible pharmacokinetic differences between the different modes of administration (DPI and MDI HFA without and with spacer) (see section on Discussion of clinical aspects).

As already mentioned, the spacer use in this study is high. In the SFC group, 33/36 (92%) of the 4-5 year olds and 102/137 (74%) of the 6-11 year olds used spacers. Similar numbers, 95% and 72%, are noted in the FP treatment group. When looking at one of the primary endpoints, the urinary cortisol excretion levels, the cortisol values seem to be more suppressed in the children using spacers. This could indicate that different amounts of the study medication (fluticasone propionate) are delivered depending on spacer use. The MAH should discuss this further in relation to the efficacy result above and the results from study SAS105519 (see section on Discussion of clinical aspects).

The safety profile is consistent with the results from earlier studies even though a large number of ECG abnormalities are reported. However, the findings are sufficiently addressed by the MAH.

VIAPED (SAM102318) study:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
VIAPED (SAM102318) Multicenter, randomised, double-blind parallel group study 8 weeks	1 inhalation of salmeterol /fluticasone propionate) DPI 50/100 mcg twice daily (Daily dose: 100/200 mcg) or 1 inhalation of fluticasone propionate) DPI 200 mcg twice daily (Daily dose: 400 mcg)	<u>Primary:</u> to prove a steroid-sparing effect of the combination of salmeterol and fluticasone propionate. Thus, non-inferiority with regard to efficacy of twice daily salmeterol/fluticasone propionate (50/100 µg) in comparison to twice daily fluticasone (200 µg) was to be demonstrated.	Children and adolescents , male or female subjects, 4-16 years of age with a diagnosis of moderate persistent bronchial asthma who have been treated with fluticasone propionate (2x 100 mcg/day) for 2 weeks during the screening period and who have been treated with ICS for at least 4 weeks prior to screening period.	281 (SFC: 137; FP: 144) 192/89 (SFC: 92/45); FP: 100/44) 4-16 years (SFC: 4-16 years, mean 9.6± 3.1 years; FP: 4-15 years, mean 9.4 ± 3.1 years)

VIAPED (SAM102318) study: was prematurely terminated. Interim analysis was performed.

This study where salmeterol/fluticasone propionate (50/100 µg) b.i.d. is compared to fluticasone propionate (200 µg) b.i.d. was prematurely terminated. Non-inferiority between the treatments is statistically confirmed for the primary endpoint. In addition, in a second step, superiority of salmeterol/fluticasone propionate compared to fluticasone propionate is statistically proven. However, all secondary efficacy outcomes are not fully supporting.

Two unexpected adverse events occurred during the study, hypoglycaemia (1 patient, SFC group), rash (1 patient, SFC group). Nevertheless, overall the data confirms the safety data from earlier studies and no SmPC modifications of the SmPC with regard to the safety is suggested from this single adverse event occurrence.

Study SAM104926:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
SAM104926 A multicentre, randomised, double-blind, double dummy, parallel group study 12 weeks	1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily (Daily dose: 100/200 mcg) or 1 inhalation of fluticasone propionate) DPI 200 mcg twice daily (Daily dose: 400 mcg)	<u>Primary:</u> to compare salmeterol/fluticasone propionate (SFC) 50/100µg twice daily with fluticasone propionate (FP) 200µg twice daily on lung function. <u>Secondary:</u> to evaluate if 'Totally Controlled' asthma is achievable and If Well Controlled' asthma is achievable in children and to compare SFC 50/100mcg bd with FP 200mcg bd on this endpoint after a 12-week treatment period.	Children, male or female subjects, 4-11 years of age with a diagnosis of bronchial asthma, who received medium doses of ICS. During the 4-week run-in period the subjects received inhaled FP 100µg twice daily and were assessed as having 'Not Well Controlled' asthma for at least 2 weeks of the run-in.	303 (SFC: 150; FP: 153) 195/108 (SFC: 97/53); FP: 98/55) 4-11 years (SFC: 4-11 years, mean 8.1 years; FP: 4-11 years, mean 8.0years)

This study in children show that treatment with salmeterol/fluticasone propionate 50/100µg bd and twice the steroid dose of fluticasone propionate (200µg bd) is statistically significantly more effective in improving the change from baseline in mean morning PEF in subjects previously uncontrolled on medium doses of inhaled corticosteroids. However, in general there are no statistically significant differences between the two treatment groups with respect to the chosen secondary endpoints.

Both treatments are well tolerated and the incidence of adverse events is similar in both groups. Thus, no new information emerged in this study that will lead to any SmPC change.

Study SFA103153:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
SFA103153 Multicenter, randomised, double-blind parallel group	1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily (Daily dose: 100/200 mcg)	<u>Primary:</u> to demonstrate that salmeterol/fluticasone propionate 50/100 mcg DISKUS BID (FSC 50/100) was superior to fluticasone propionate 100 mcg DISKUS BID (FP 100) in	Adults and adolescents of African descent, male or female subjects, 12 to 65 years of age with persistent asthma, and were symptomatic while	475 (SFC: 239; FP: 236) 182/293 (SFC: 96/143);

study 52 weeks	or 1 inhalation of fluticasone propionate) DPI 100 mcg twice daily (Daily dose: 200 mcg)	controlling the asthma exacerbation rate. <u>Secondary:</u> to determine whether the measures of asthma control (AM and PM peak expiratory flow [PEF], asthma symptoms and use of rescue albuterol) differed in subjects who received FSC 100/50 compared with those who received FP 100 alone.	taking an ICS. After completing the two-week screening period, eligible subjects discontinued taking their baseline ICS and were provided open-label fluticasone propionate 250 mcg DISKUS (FP 250) to take twice daily for four weeks. Subjects who completed the double-blind treatment period entered a four week run-out period and were provided open-label FP 250 to take twice daily.	FP: 86/150 12-63 years (SFC: 12-61 years, mean 31.5 years; FP: 12-63 years, mean 32.2 years) <i>African American:</i> 97 % (SFC); 98% (FP)
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In subjects, 12-65 years, of African descent no statistically significant differences in the asthma exacerbation rate per year are observed between the treatments salmeterol/fluticasone propionate 50/100 DISKUS (SFC 50/100) twice daily and fluticasone propionate 100 DISKUS (FP 100) twice daily. The rate of asthma exacerbations in both study arms was low, 0.449 for SFC 50.100 and 0.529 for FP 100. Few adolescent subjects are included in this study and no subanalysis for this group is available. Thus, no real conclusions can be drawn from this study.

However, there are no unexpected adverse events that seem to suggest a different safety profile.

Study SFA100062:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
SFA100062 Multicenter, randomised, double-blind parallel group study 16 weeks	1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily (Daily dose: 100/200 mcg) or 1 inhalation of salmeterol 50 mcg twice daily (Daily dose: 100 mcg)	<u>Primary:</u> to evaluate lung function as assessed by AM PEF AUC relative to baseline [AUC(bl)] in subjects with different genotypes over 16 weeks of treatment with FSC DISKUS 50/100mcg BID. <u>Secondary:</u> to evaluate lung function as assessed by AM PEF AUC(bl) and other measures in other ADRB2 genotypes in the SM and FSC treatment groups over 16 weeks of treatment.	Adults and adolescents , male or female subjects, at least 12 years of age, with asthma, who have either a B16-Arg/Arg, a B16-Gly/Gly or a B16-Arg/Gly genotype and are Treated With Fluticasone Propionate/Salmeterol DISKUS™ Combination Product 100/50mcg or Salmeterol DISKUS 50mcg BID.	544 (<u>SFC:</u> 272; Arg/Arg:89 Gly/Gly: 91 Arg/Gly: 92 <u>SM:</u> 272 Arg/Arg:90 Gly/Gly:92 Arg/Gly:90) 202/166 (<u>SFC:</u> 96/176; <u>SM:</u> 106/166) 12-74 years (<u>SFC:</u> 12-73; mean 31-34 years. <u>SM:</u> 12-74; mean 30-35 years)

Study SFA100062: The Arg/Arg genotype (occurs at a frequency of about 15% in the general population), Gly/Gly genotype (occurs with approximately a 35% frequency) and the Gly/Arg genotype (occurs with approximately a 50% frequency).

Overall, there are no indications of any genotype dependent effect on efficacy or safety. Overall, the frequency and type of adverse events reported by subjects were similar across genotypes in each treatment arm. However, no specific subanalysis is performed for the adolescent group. Thus, with respect to the

adolescents group no real conclusion can be drawn. Nevertheless, no new significant findings are observed in this study.

Study SAS105519:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
<p>SAS105519</p> <p>Multicenter, repeat-dose, open-label, randomised, incomplete block design study</p> <p>21 days</p>	<p>2 inhalations of Advair (salmeterol/fluticasone propionate) HFA 21/45 twice daily with or without a Spacer (Daily dose: 82/180 mcg)</p> <p>or</p> <p>1 inhalation of Advair (salmeterol/fluticasone propionate) Diskus 50/100 twice daily (Daily dose: 100/200 mcg)</p>	<p><u>Primary</u> to assess the pharmacodynamics of fluticasone propionate (FP) as measured by serum cortisol levels following administration of 2 X Advair HFA 45/21, 2 X Advair HFA 45/21 using an Aerochamber Plus Spacer, and Advair Diskus 100/50. <u>Secondary</u> 1) to assess the systemic exposure of FP and salmeterol (SAL) following administration of 2 X Advair HFA 45/21, 2 X Advair HFA 45/21 using an Aerochamber Plus Spacer, and Advair Diskus 100/50; 2) to assess the effect of 2 X Advair HFA 45/21, 2 X Advair HFA 45/21 using an Aerochamber Plus Spacer, and Advair Diskus 100/50 on heart rate, blood pressure, and ECG measurements.</p>	<p>Children, male and pre-menarchial female subjects with mild asthma (PEF > 75% predicted) aged 4 - 11 years, inclusive, and weighing at least 11 kg at screening, were eligible for this study. Subjects were to have asthma control via regular or intermittent non-steroidal asthma medication (e.g., short acting beta-agonist (SABA) or montelukast) for at least three months prior to entry in to the study; subjects were not permitted to be taking a long acting beta agonist.</p>	<p>31</p> <p>24/7</p> <p>4-11 years (mean 7.2 ± 2.4 years; 15 (48%) subjects were ≤7 years of age.</p>

Reductions of cortisol levels 14%, 13% and 22% are observed in the Advair HFA, Advair Diskus and Advair HFA with a Spacer treatment groups, respectively. Even though not statistically significant, the reductions indicate that different amounts of the study medication (fluticasone propionate) are delivered.

It appears favourable to use the Aerochamber plus spacer when treating children with salmeterol/fluticasone propionate as HFA pressurised inhalation suspension. This information is partly given in the SmPC (for patients who has difficulties in coordinating actuation and inhalation) but no information on the pharmacokinetic differences is presented. As the individual effect is so unpredictable this may be acceptable, however, the mean effect could also be given in the SmPC. Also, the SmPC does not give clear information that use may be advantageous from an efficacy perspective. The SmPC mainly focuses on safety (systemic adverse effects).

The applicant was asked to present the pharmacokinetics of fluticasone propionate given as Advair HFA versus age to enable assessment of the age effect and discuss whether any special recommendations are needed in the SmPC with respect to formulations/use of spacer and age. In addition, based on all available data including previous studies, the pharmacokinetic mean differences between the different modes of administration the MAH was asked to present in section 5.2 of the SmPC together with a description of the variability in individual effect. Cross-references should be made from sections 4.2 and 4.4 to this section (i.e. 5.2) (see section on Discussion of clinical aspects)..

In this small study, no unexpected adverse events are observed.

Study ADA103578:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
ADA103578 Multicenter, randomised, double-blind, triple-dummy, placebo-controlled, parallel group, 4 weeks	1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily (Daily dose: 100/200 mcg) or Montelukast (10mg QD), Tablets or 1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily + Montelukast (10mg QD), Tablets (Daily dose: 100/200 mcg) or 1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily + Fluticasone propionate aqueous <i>nasal spray</i> (FPANS) 200mcg QD (Daily inhalation dose: 100/200 mcg) Daily total FP dose: 600 mcg)	<u>Primary:</u> to demonstrate that fluticasone propionate/salmeterol combination product (FSC) 100/50mcg BID (available as ADVAIR DISKUS®) was superior to montelukast (MON) 10mg QD (available as Singulair) as monotherapy for asthma, and that MON administered concurrently with FSC added no additional benefit to FSC alone in improving asthma control. <u>Secondary:</u> to demonstrate that in the presence of FSC, fluticasone propionate aqueous nasal spray (FPANS) 200mcg QD (available as FLONASE™) was superior to MON for control of rhinitis symptoms.	Adults and adolescents, male or female subjects, 15-74 years with persistent asthma (FEV1 between 65%-95%) and a diagnosis of seasonal allergic rhinitis. Subjects were to have asthma control via SABA alone, ICS, or non-ICS at a fixed dosing regimen for at least one month prior to the screening visit.	660 (SFC+FPANS: 168 SFC+MON: 165 SFC: 157 MON: 170) 208/452 (SFC+FPANS: 52/116 SFC+MON: 45/120 SFC: 49/108 MON: 62/108) 15-73 years (SFC+FPANS: 15-70 (mean 36±13) years; SFC+MON: 15-71 (mean 37±12) years; SFC: 15-72 /mean 37±14) years; MON: 15-73 (mean 37± 14) years. <i>6-14 subjects/ arm were ≤16 years of age in the FSC groups. 10-20 subjects/ arm were ≤18 years of age in the FSC groups</i>

The subjects, 15-76 years, in this short treatment study had persistent asthma and a diagnosis of seasonal allergic rhinitis. A limited number of adolescent subjects are, however, included in the different treatment arms. Only 6-12% (10-20 subjects/ arm) of the studied population are between 15 to 18 years included. In the ≥15 to ≤16 year category, 6-14 subjects per arm are included. Thus, the data on adolescents is limited and no real conclusions for the age group can be drawn from this study. However, no unexpected adverse events are reported during this short course of this study.

Study ADA103575:

Table 1, cont., Overview of the submitted clinical studies (Diskus=DPI, Evohaler=MDI)

Protocol Number; Study Design; Duration of Treatment	Study Treatments (Daily dose SFC in bold)	Objective	Subject Population	No. of Subjects; Males/Females; Age Range
ADA103575 Multicenter,	1 inhalation of salmeterol/fluticasone propionate) DPI 50/100	<u>Primary:</u> to demonstrate that fluticasone propionate/ salmeterol combination product	Adults and adolescents, male or female subjects, 15-76 years with	725 (SFC+FPANS: 182

<p>randomised, double-blind, triple-dummy, parallel group,</p> <p>4 weeks</p>	<p>mcg twice daily (Daily dose: 100/200 mcg) or Montelukast (10mg QD), Tablets or 1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily + Montelukast (10mg QD), Tablets (Daily dose: 100/200 mcg) or 1 inhalation of salmeterol/fluticasone propionate) DPI 50/100 mcg twice daily + Fluticasone propionate aqueous <i>nasal spray</i> (FPANS) 200mcg QD (Daily inhalation dose: 100/200 mcg) Daily total FP dose: 600 mcg)</p>	<p>(FSC) 100/50mcg BID (available as ADVAIR DISKUS®) was superior to montelukast (MON) 10mg QD (available as Singulair) as monotherapy for asthma, and that MON administered concurrently with FSC added no additional benefit to FSC alone in improving asthma control. <u>Secondary:</u> to demonstrate that in the presence of FSC, fluticasone propionate aqueous nasal spray (FPANS) 200mcg QD (available as FLONASE™) was superior to MON for control of rhinitis symptoms.</p>	<p>persistent asthma (FEV1 between 65%-95%) and a diagnosis of seasonal allergic rhinitis. Subjects were to have asthma control via SABA alone, ICS, or non-ICS at a fixed dosing regimen for at least one month prior to the screening visit.</p>	<p>SFC+MON: 182 SFC: 180 MON: 181)</p> <p>276/449 (SFC+FPANS: 62/120 SFC+MON: 67/115 SFC: 78/102 MON: 69/112)</p> <p>15-76 years (SFC+FPANS: 15-67 (mean 35±13) years; SFC+MON: 15-66 (mean 33±14) years; SFC: 15-76 /mean 35±15) years; MON: 15-69 (mean 34± 12) years. 16-20 subjects/ arm were ≤16 years of age in the FSC groups. 25-33 subjects/ arm were ≤18 years of age in the FSC groups</p>
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This study (identical in design to ADA103578), with four treatment arms and a duration of 4 weeks, was conducted in subjects (15-76 years) who had persistent asthma and a diagnosis of seasonal allergic rhinitis. Asthma superiority is demonstrated for SFC over MON treatment; however, asthma equivalence could not be demonstrated for FSC and FSC+MON. Thus, the conclusions that can be drawn from this study are limited. Although with regard to safety, no unexpected adverse events occurred during the short treatment time.

Overall conclusions

Pharmacokinetics

It appears favourable to use the Aerochamber plus spacer when treating children with salmeterol/fluticasone propionate as HFA pressurised inhalation suspension. This information is partly given in the SmPC (for patients who have difficulties in coordinating actuation and inhalation) but no information on the pharmacokinetic differences is presented. As the individual effect is so unpredictable this may be acceptable, however, the mean effect could also be given in the SmPC. Also, the SmPC does not give clear information that use may be advantageous from an efficacy perspective. The SmPC mainly focuses on safety (systemic adverse effects).

Efficacy

The efficacy of salmeterol/fluticasone propionate in children and adolescents with asthma is further confirmed in the submitted studies. However, for children a clearer recommendation in the SmPC is needed with respect to formulation/use of spacer and age.

Safety

Salmeterol/fluticasone propionate, provided either as MDI or DPI, is well tolerated by the patients and the adverse effects are well known. Only one unexpected adverse event, hypoglycaemia, occurred. However,

overall the studies confirm the well established safety profile from earlier studies. Thus, there is no new significant information leading to modifications of the SmPC with regard to adverse events.

Discussion of clinical aspects

On 17 June, 2009 the Rapporteur circulated the day 70 assessment report for the EU Worksharing Procedure for paediatric data for Salmeterol/fluticasone propionate. Comments were received from Member States and a List of Questions was subsequently sent to the MAH.

The List of Questions was as follows:

1. The MAH should present the pharmacokinetics of fluticasone propionate given as Advair (salmeterol/fluticasone propionate) HFA versus age to enable assessment of the age effect and discuss whether any special recommendations are needed in the SmPC with respect to formulation/use of spacer and age (study SAS105519). In addition, based on all available data including previous studies, the pharmacokinetic mean differences between the different modes of administration (SFC DPI, SFC MDI HFA without spacer, and SFC MDI HFA with spacer) should be presented in section 5.2 of the SmPC together with a description of the variability in individual effect. Cross-references should be made from sections 4.2 and 4.4 to this section (i.e. 5.2).

2. The MAH should perform a subanalysis with respect to spacer use in the SFC and FP treatment groups in study SFA106484. The MAH should further discuss the results in relation to the possible pharmacokinetic differences between the different modes of administration (DPI, MDI HFA without and with spacer). In addition, when looking at one of the primary endpoints, the urinary cortisol excretion levels, the levels seem to be more suppressed in the children using spacers. This could indicate that different amounts of the study medication (fluticasone propionate) are delivered depending on spacer use (MDI with and without spacer). The MAH should further discuss this in relation to the questions raised above. Please see also question 1.

3. Following on from the Question 2, the MAH is requested to discuss whether any dosage adjustment can be recommended when SFC MDI HFA is used with a spacer.

4. In study SAS105519 the systemic exposure to fluticasone propionate was markedly lower in the Advair HFA group. Please elaborate on indications for reduced efficacy in this group (e.g. with regard to PEF measurements) warranting a stronger recommendation for the use of a spacer device.

5. Some EU countries have approved Seretide nationally. SmPC wording of sections 4.1 and 4.2 from each nationally approved SmPC was not submitted. The MAH should discuss if the indication and posology in these EU countries are similar to the indication and posology that have been approved through the MRP procedures.

On 2 October 2009 the MAH submitted the Applicant's Responses to the Request for Supplementary Information. On 1 December, 2009 the Rapporteur circulated the second assessment report. No additional data were requested.

III. RAPPORTEUR'S FINAL OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Pharmacokinetics

It appears favourable to use the Aerochamber plus spacer when treating children with salmeterol/fluticasone propionate as HFA pressurised inhalation suspension. The MAH has agreed to present a summary of study SAS105519 in Section 5.2 of the Salmeterol/FP Inhaler SmPC with a cross-reference in Section 4.2.

Efficacy

The efficacy of salmeterol/fluticasone propionate in children and adolescents with asthma is further confirmed in the submitted studies. However, for children a clearer recommendation in the SmPC is needed with respect to formulation/use of spacer and age. Thus, a modification of section 4.2 is proposed.

Safety

Salmeterol/fluticasone propionate, provided either as MDI or DPI, is well tolerated by the patients and the adverse effects are well known. Only one unexpected adverse event, hypoglycaemia, occurred. However, overall the studies confirm the well established safety profile from earlier studies. Thus, there is no new significant information leading to modifications of the SmPC with regard to adverse events.

➤ Recommendation

The MAH is encouraged to submit a type II variation to include pharmacokinetic data and information regarding spacer use and age. The studies provided by the applicant are considered sufficient to include new information in sections 4.2 and 5.2 of the SmPC.

In addition, the name of the spacer device which has been tested together with Seretide Evohaler should be included in the SmPC and the package leaflet (PL).

SmPC

The following SmPC changes are proposed:

Section 4.2

Children <12 years old may have difficulties synchronising aerosol actuation with inspiration of breath. Use of a spacer device with Seretide inhaler is recommended in patients who ~~find it~~ have, or are likely to have difficulties to synchronise aerosol coordinate actuation with inspiration of breath. A recent clinical study has shown that paediatric patients using a spacer achieved exposure similar to adults not using spacer and paediatric patients using Diskus, confirming that spacers compensate for poor inhaler technique (see Section 5.2).

Section 5.2

Paediatric population

The effect of 21 days of treatment with Seretide Inhaler 25/50mcg (2 inhalations twice daily with or without a spacer) or Seretide Diskus 50/100mcg (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to fluticasone propionate was similar for Seretide Inhaler with spacer (107pg hr/mL [95% CI: 45.7, 252.2]) and Seretide Diskus (138pg hr/mL [95% CI: 69.3, 273.2]), but lower for Seretide Inhaler (24pg hr/mL [95% CI: 9.6, 60.2]). Systemic exposure to salmeterol was similar for Seretide Inhaler, Seretide Inhaler with spacer, and Seretide

Diskus (126 pg hr/mL [95% CI: 70, 225], 103 pg hr/mL [95% CI: 54, 200], and 110 pg hr/mL [95% CI: 55, 219], respectively).

Rapporteur's comment (SmPC section 5.2):

The data which may be of most interest and which is related to section 4.2 recommendations should preferably be given first. The variability in estimated AUCs should be presented as standard deviation instead of 95% CIs.

Rapporteur's comment:

In addition, the name of the spacer device which has been tested together with Seretide Evohaler should be included in the SmPC.

Package Leaflet

Rapporteur's comment:

The name of the spacer device which has been tested together with Seretide Evohaler should be included in the PL.