Public Assessment Report
Scientific discussion

Salmeterol/Fluticasone Sandoz
(salmeterol xinafoate, fluticasone propionate)

SE/H/1323/03/DC

This module reflects the scientific discussion for the approval of Salmeterol/Fluticasone Sandoz. The procedure was finalised on 2015-03-19. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Salmeterol/Fluticasone Sandoz, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Sandoz A/S applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, HU and RO as concerned member states (CMS).

The applications are also extensions, addition of a new strength, of previously authorised Salmeterol/Fluticasone Sandoz, inhalation powder, pre-dispensed, 50 microgram/500 microgram/dose (SE/H/1323/02/DC).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Seretide Diskus mite inhalation powder, pre-dispensed, 50 microgram/100 microgram/dose, authorised in Sweden since 1998, with GlaxoSmithKline AB as marketing authorisation holder.

The reference product used in the bioequivalence studies are Seretide Accuhaler, 50/500 microgram/dose, 50/250 microgram/dose from UK (Glaxo Wellcome UK Ltd) and Viani mite Diskus, 50/250 microgram/dose from DE (GlaxoSmithKline GmbH&Co KG).

The 50 microgram/250 microgram strength was included in the originally submitted application for Salmeterol /Fluticasone Sandoz but was withdrawn during the procedure due to PSRPH raised by one of the CMS and only the 50/500 µg strength was approved.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substances has been adequately proven and their physico-chemical properties are sufficiently described.

The manufacture of the drug substances has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specifications include relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.
II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

According to the guideline “Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents” (CPMP/EWP/4151/00 rev 1 guideline; “OIP guideline”) a step-wise approach should be considered when demonstrating therapeutic equivalence. The first step consists of pharmaceutical data, the second step of pharmacokinetic data and the third step is represented by pharmacodynamic/clinical efficacy and safety data. In this case the quality data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based on in vitro data and in vivo studies are needed for demonstration of therapeutic equivalence. In this application the aim of the Applicant has been to demonstrate therapeutic equivalence using pharmacokinetic data in support of efficacy and safety.

The clinical development program and the relation to regulatory guidance are presented in Table 1 below.
Table 1. Study package overview and regulatory guidance

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Dose</th>
<th>Assessment of equivalence (safety/efficacy) via:</th>
<th>Ref. to guidance/other pertinent information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal studies</strong></td>
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</table>

PWDI-7  (Safety study, no charcoal) | 50/500 SX/FP 2 puffs | BE safety: AUC and Cmax CI 80-125%; BE efficacy: SX AUC 30 | CPMP/EWP/4151 Rev. 1 Addendum No.1 to study report; Ref. (7), (4), (6) |

PWDI-9 (Efficacy study, with charcoal) | 50/250 SX/FP 2 puffs | BE efficacy: AUC and Cmax CI 80-125% | CPMP/EWP/4151 Rev. 1 |

PWDI-17 (Safety study, no charcoal) | 50/250 SX/FP 2 puffs | BE safety: AUC and Cmax CI 80-125% after FPD correction; | CPMP/EWP/4151 Rev. 1 Guidance for the Industry FDA CDER 1997 CPMP/QWP/98/96 CPMP/EWP/QWP/1401/98 Rev. 1 |

**Supportive studies** | | | |

DPI-1 | 50/500 SX/FP 50/100 SX/FP 1 puff bid | efficacy and safety of the test products vs. the originator products in adolescent and adult patients with moderate-to-severe persistent asthma; 12-week, double-blind, double-dummy, parallel-group study | CPMP/EWP/4151 Rev. 1 |

Flow rate study not named | not applicable | flow profiles in healthy subjects and patients with asthma and COPD, comparison of devices | not applicable |

Note: With respect to fluticasone, PK data obtained with charcoal (efficacy design) can be extrapolated to total systemic exposure as explained above and PK data obtained without charcoal (safety design) also to efficacy as explained above.

In addition to the studies listed in Table 1 above additional studies have been conducted with a 50/100 SX/FP dose strength (Study IDs: PWDI-6 and DPI-2). Further, a pilot PK study (Study ID: PWDI-11) with a 50/250 SX/FP dose strength (2 different active pharmaceutical ingredient sources: Test A and Test B), when applied as 1 puff bid has been conducted.

**IV.2 Pharmacokinetics**

Two pivotal pharmacokinetic studies, PWDI-9 and PWDI-17, have been performed with the 50/250 μg strength. Additional studies with other strengths have been used in an in vitro – in vivo correlation (IVIVC) which is supportive in the current application. This concerns study PWDI-7 (conducted with the already approved 50/500 μg strength) and PWDI-6 (with a 50/100 μg strength).

The pharmacokinetic studies were single-dose, crossover bioequivalence studies conducted in healthy volunteers. In general, the design of the studies was adequate. Extrapolation of results from a PK study performed with healthy volunteers to a patient population is acceptable if there is no flow rate dependency of FPD for test and reference product or if the flow rate dependency is similar. In this case there is a slight flow rate dependency over the investigated range (30 to 90 L/min). However, both test and reference product are comparable and the dependency is considered similar. Hence, the use of healthy volunteers is acceptable.
Pharmacokinetic studies aim at demonstrating similar pulmonary deposition and similar total systemic exposure between a “new inhalation generic product” and the originator. According to the OIP guideline, bioequivalence studies with charcoal blockade could be used to compare pulmonary deposition as a surrogate for efficacy. In addition, bioequivalence studies without charcoal blockade could be used to compare systemic exposure as a surrogate for safety. However, for active substances with negligible gastrointestinal absorption, studies with active charcoal may be sufficient in the assessment of therapeutic equivalence. Due to pre-systemic metabolism, the oral availability of fluticasone is less than 1% and considered to be negligible. For salmeterol the contribution of GI-absorbed substance is on the other hand not insignificant.

Bioequivalence between Salmeterol/Fluticasone Sandoz 50 μg/250 μg and Seretide was evaluated in study PWDI-9 (with charcoal blockade) and PWDI-17 (without charcoal blockade). Taking into account the lack of bioequivalence for fluticasone Cmax in Study PWDI-9 when analysed according to the study protocol, the second study, PWDI-17, was conducted. In this study bioequivalence was assessed on the basis of a fine particle dose (FPD) correction to account for unpredictable batch-to-batch and/or within batch variability of the reference product as predefined in the protocol.

For salmeterol bioequivalence was demonstrated for AUC and Cmax when administered with active charcoal and hence similarity in efficacy can be concluded. When salmeterol was administered without active charcoal to evaluate systemic safety, bioequivalence was demonstrated for AUC while Cmax was lower for Salmeterol/Fluticasone Sandoz compared to Seretide. With respect to safety a lower Cmax is not a disadvantage and it could be concluded that the safety regarding salmeterol has been sufficiently assured.

For fluticasone bioequivalence could not be demonstrated in any of the studies without FPD-correction. In study PWDI-9 Cmax was 29% lower for the test compared to the reference product and in study PWDI-17 (without FPD-correction) AUC and Cmax of the test product was 21% and 28% lower respectively. The difficulties in demonstrating bioequivalence may be explained by variability in FPD of the reference product between batches and also over time. After FPD-correction of PK-results in study PWDI-17, as pre-specified in the protocol, bioequivalence was sufficiently assured also for fluticasone.

To support the FPD-correction in Study PWDI-17 an in vitro - in vivo correlation (IVIVC) was established. For fluticasone a correlation between FPD and AUC and also between FPD and Cmax, both for the test and the reference product was shown. By using the established correlation, a normalisation to the median FPD of the entire FPD-distribution of the reference and the test product respectively was performed. With this method the PK-data was corrected in order to predict results expected for a median test or reference batch respectively. When the PK-results from study PWDI-17 was normalised as outlined above, bioequivalence was demonstrated for fluticasone AUC and Cmax. This approach was accepted to overcome difficulties in finding representative batches, and bioequivalence regarding fluticasone was considered to have been sufficiently demonstrated in study PWDI-17.

Overall pharmacokinetic conclusion
Therapeutic equivalence between Salmeterol/Fluticasone Sandoz and Seretide 50 μg/250 μg has been sufficiently demonstrated through pharmacokinetic data.

IV.3 Pharmacodynamics
The drug product contains Salmeterol and Fluticasone propionate which have differing modes of action. Salmeterol is a selective long-acting (12 hour) beta-2-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor. Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta-2-agonists. Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, without the adverse effects observed when corticosteroids are administered systemically. Both active substances are considered well known.

IV.4 Clinical efficacy and safety

The Applicant has submitted two clinical studies, Study 2006-56-DPI-1 and VR315/1/001 (Flow rate study Inamed) to this application.

The phase III clinical study Study 2006-56-DPI-1 evaluated the efficacy and safety of Salmeterol/Fluticasone DPI HEXAL (Salmeterol/Fluticasone Sandoz) versus SeretideTM AccuhalerTM in adolescent and adult patients with moderate-to-severe persistent asthma (n=555). The study was a 12-week, multicenter, randomized, double-blind, double-dummy, parallel group study. Patients were treated with a fixed dose combination of salmeterol xinafoate (SX) and fluticasone propionate (FP) delivered by a dry powder for inhaler (DPI) of either SX/FP 50/100 μg or of SX/FP 50/500 μg per inhalation and the aim of the study was demonstrate therapeutic equivalence. No placebo arm was included. The study was submitted by the applicant as supportive patient data because in the study a statistical significant dose response could not be shown neither for the test nor for the reference product. Therefore, study DPI-1 cannot be considered to be a pivotal clinical study on which the therapeutic equivalence can be based on.

In addition a flow rate study VR315/1/001 (Flow rate study Inamed) was performed to obtain flow profiles in healthy subjects and patients with asthma and chronic obstructive pulmonary disease (COPD). This study was an open-label, randomised, cross-over design and examined the inhalation flow rate as a function of time. The study included a comparison between the originator inhaler device (Seretide Diskus) and the inhaler device of the applicant (Forspiro) in patients with mild persistent asthma, with moderate persistent asthma, with severe persistent asthma, with severe COPD, children with asthma or recurrent obstructive bronchitis and healthy volunteers. The total number of subjects was 60 in the study. The highest maximal inhalation flow rates were achieved by the three subpopulations of adolescent/adult asthmatics and the healthy volunteer group. Comparable but slightly lower values were reached by severe COPD patients, and the lowest values were seen for the subpopulation of asthmatic children. The inhalation rates were comparable between the test and reference devices in each patient/subject group, although there was a slight trend for higher inhalation rates with the test device. The mean flow rates were lowest in the asthmatic children and severe COPD patients. However, all subjects generated a minimum effective flow of 30 L/min. To conclude, the use of healthy volunteers in the conducted PK studies is considered acceptable based on the presented data.

With respect to adolescents (12-17 years), a total of 48 subjects were included in the study 2006-56-DPI-1 with 10-14 subjects in each treatment arm. The results indicate possibly higher or comparable results when compared to adults for the primary endpoint change in mean FEV1. Taken together, it is considered that a sufficient number of adolescents have been included in the study. If therapeutic equivalence can be demonstrated with the use of
pharmacokinetic data it is considered acceptable that Salmeterol/Fluticasone Sandoz can be used in subjects from the age of 12 years and older. To conclude, study DPI-I cannot be considered to be a pivotal clinical study on which the therapeutic equivalence is based on. Thus, quality data and or pharmacokinetic data are needed to support the therapeutic equivalence.

IV.5 Risk Management Plans

The Applicant has submitted an updated Risk Management Plan (RMP), version no 1.2, dated 10 July, 2014 with the below Summary of Safety Concerns and corresponding updates in relevant sections of the RMP:

**Summary of Safety Concerns; RMP version 1.2, dated 10 July 2014**

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Respiratory-related events or deaths</th>
<th>Pneumonia</th>
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<tr>
<td></td>
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<td>Cushing's syndrome and adrenal suppression</td>
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<td>Growth retardation in paediatrics</td>
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<td></td>
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<td>Drug-interaction with CYP450 3A4 inhibitors</td>
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<td>Hypersensitivity reactions including anaphylactic reactions</td>
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<td>Arrhythmias</td>
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<td>Angina</td>
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<tr>
<td>Important potential risks</td>
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<td>Off-label use in children below 12 years old</td>
</tr>
<tr>
<td>Missing information</td>
<td></td>
<td>Patients with hepatic impairment</td>
</tr>
</tbody>
</table>

**Pharmacovigilance Plan**
No special important risks or potential risks have been identified for salmeterol-fluticasone, which require additional pharmacovigilance activities other than routine. This is endorsed.

**Risk minimization measures by safety concern**
No special important risks or potential risks have been identified for salmeterol-fluticasone, which require additional risk minimization activities other than routine. This is endorsed.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Airflusal Forspiro 500/50 microgram inhalation powder, predisposed, SE/H/1321/02/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
This application concerns Salmeterol/Fluticasone Sandoz, inhalation powder, pre-dispensed, 50/250 µg.

The application for Salmeterol/Fluticasone Sandoz is a hybrid application and evaluated in a step-wise approach according to the guideline CPMP/EWP/4151/00 Rev.1. In this case the quality data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based on in vitro data and in vivo studies are needed for demonstration of therapeutic equivalence. In this application the aim of the Applicant has been to demonstrate therapeutic equivalence using pharmacokinetic data in support of efficacy and safety.

Based on pharmacokinetic data salmeterol efficacy was shown to be similar and safety not worse for Salmeterol/Fluticasone Sandoz compared to Seretide. For fluticasone bioequivalence was demonstrated after an IVIVC had been established and the PK-data were normalised to reflect a representative batch. Hence, based on PK-data, similarity in efficacy and safety of fluticasone has been sufficiently demonstrated.

Therapeutic equivalence between Salmeterol/Fluticasone Sandoz and Seretide has been sufficiently demonstrated through pharmacokinetic data.

The Applicant has submitted a supportive clinical study (2006-56-DPI-1). This study was conducted using the higher strength 50 µg/500 µg and thus it does not add to the current application. Nevertheless, as therapeutic equivalence can be demonstrated with the use of pharmacokinetic data it is considered acceptable that Salmeterol/Fluticasone Sandoz can be used in subjects from the age of 12 years and older.

Conclusion
To conclude, the risk/benefit ratio is considered positive and Salmeterol/Fluticasone Sandoz, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose, and is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment
N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The Decentralised procedure for Salmeterol/Fluticasone Sandoz, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose, was positively finalised on 2015-03-19.
# Public Assessment Report – Update

<table>
<thead>
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<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
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