Public Assessment Report
Scientific discussion

Salmeterol/Fluticasone Hexal
(salmeterol xinafoate, fluticasone propionate)

SE/H/1322/02/DC

This module reflects the scientific discussion for the approval of Salmeterol/Fluticasone Hexal. The procedure was finalised at 2013-12-05. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Salmeterol/Fluticasone Hexal inhalation powder, pre-dispensed, 50 microgram/500 microgram/dose is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Hexal A/S applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member states (CMS).

During the procedure, the Applicant withdrew the strength 50/250 µg.

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).

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Salmeterol/Fluticasone Hexal is presented in the form of a pre-dispensed inhalation powders containing 50 microgram/dose of salmeterol (as salmeterol xinafoate) and 250 microgram/dose of fluticasone propionate. The excipient is lactose monohydrate. The powder formulation is packed in/filled in OPA/Al/PVC-Al blisters.

II.2 Drug Substance

The salmeterol xinafoate and fluticasone propionate have monographs in the Ph Eur.

Both salmeterol xinafoate and fluticasone propionate consists of a white, crystalline powder which is poorly soluble in water. The structure of salmeterol xinafoate and fluticasone propionate have been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, chirality, is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.
II.3 Medicinal Product

Salmeterol/Fluticasone Hexal is pre-dispensed inhalation powders formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility, hygroscopic properties, polymorphism, and stability.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25 °C.

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

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 (Study type)</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>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWDI-7 (Safety study, no charcoal)</td>
<td>50/500 SX/FP 2 puffs</td>
<td>BE safety: AUC and Cmax CI 80-125%; BE efficacy: SX AUC 30</td>
<td>CPMP/EWP/4151 Rev. 1 Addendum No. 1 to study report; Ref. (7), (4), (6)</td>
</tr>
<tr>
<td>PWDI-9 (Efficacy study, with charcoal)</td>
<td>50/250 SX/FP 2 puffs</td>
<td>BE efficacy SX see also PWDI-9; same dose of SX as in PWDI-7 BE efficacy: AUC and Cmax CI 80-125%</td>
<td>CPMP/EWP/4151 Rev. 1</td>
</tr>
<tr>
<td>PWDI-17 (Safety study, no charcoal)</td>
<td>50/250 SX/FP 2 puffs</td>
<td>BE safety: AUC and Cmax CI 80-125% after FPD correction;</td>
<td>CPMP/EWP/4151 Rev. 1 Guidance for the Industry FDA CDER 1997 CPMP/QWP/604/96 CPMP/EWP/QWP/1401/ 98 Rev. 1</td>
</tr>
</tbody>
</table>

| 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 inamed** | 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.*

Note! Study PWDI-9 and PWDI-17 were only relevant for the 50 μg/250 μg strength which was withdrawn during the procedure.

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.

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.
IV.1 Pharmacokinetics

Bioequivalence between Salmeterol/Fluticasone Hexal 50 μg/500 μg and Seretide was evaluated in study PWDI-7. The study was a single-dose, four-period, replicate, crossover study in 59 healthy volunteers under fasting conditions. The test drugs were administered without the administration of active charcoal. In each period a single-dose of 100 μg/1000 μg salmeterol/fluticasone (=2 inhalations) of the test or reference drug was administered. Blood-samples were collected frequently after drug administration in order to catch the early Cmax of salmeterol and up to 12 h after drug administration. Plasma concentrations of salmeterol and fluticasone were analysed using a validated LC/MS/MS-method. The overall study design was 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 the study could also be used as support of similar efficacy of fluticasone. For salmeterol the contribution of GI-absorbed substance is on the other hand not insignificant. An additional post-hoc analysis of $AUC_{0-30\ min}$ for salmeterol was therefore presented as a measure of pulmonary deposition in support of salmeterol efficacy. This was accepted, given the very fast absorption of salmeterol, with maximal plasma concentrations reached after 2-5 min after oral inhalation.

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.

As shown in the tables below bioequivalence was demonstrated for AUC and Cmax for both active substances and also for $AUC_{0-30\ min}$ for salmeterol.

**Table 2. Salmeterol pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) after oral inhalation of 2x 50 μg/500 μg salmeterol/fluticasone, n=59.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ pg*h/ml</th>
<th>$C_{max}$ pg/ml</th>
<th>$t_{max}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>328.57 ± 109.00</td>
<td>297.50 ± 111.29</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td>Reference</td>
<td>282.11 ± 90.83</td>
<td>265.69 ± 84.21</td>
<td>0.06 ± 0.04</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

1.1592 (1.1243-1.1952) 1.1041 (1.0574-1.1528)

*AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours

$C_{max}$ maximum plasma concentration

$t_{max}$ time for maximum plasma concentration

*calculated based on ln-transformed data
Table 3. Fluticasone pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\textsubscript{max}) after oral inhalation of 2x 50 μg/500 μg salmeterol/fluticasone n=59.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-t} pg\textsubscript{h}/ml</th>
<th>C\textsubscript{max} pg/ml</th>
<th>t\textsubscript{max} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1083.11 ± 311.76</td>
<td>148.03 ± 45.16</td>
<td>1.66 ± 1.12</td>
</tr>
<tr>
<td>Reference</td>
<td>1166.84 ± 260.88</td>
<td>176.53 ± 49.99</td>
<td>1.40 ± 0.94</td>
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</table>

*Ratio (90% CI)

<table>
<thead>
<tr>
<th>*</th>
<th>0.9129</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.8791-0.9479)</td>
<td>0.8340</td>
</tr>
<tr>
<td>(0.8022-0.8671)</td>
<td></td>
</tr>
</tbody>
</table>

AUC\textsubscript{0-t} area under the plasma concentration-time curve from time zero to t hours
C\textsubscript{max} maximum plasma concentration
t\textsubscript{max} time for maximum plasma concentration

*calculated based on in-transformed data

Table 3: Bioequivalence results for salmeterol AUC\textsubscript{0-30min}. Study PWDI-7.

<table>
<thead>
<tr>
<th>AUC \textsubscript{0-30min}</th>
<th>Point estimator</th>
<th>Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>N subjects = 59</td>
<td>118.67%*</td>
<td>114.40% - 123.09%*</td>
</tr>
<tr>
<td>N subjects = 61</td>
<td>119.34%*</td>
<td>115.12% - 123.71%*</td>
</tr>
</tbody>
</table>

Method: ANOVA; CV: Coefficient of variation; *Parametric confidence interval and point estimator; T/R: Ratio Test versus Reference

Conclusion: Bioequivalence was demonstrated for AUC and Cmax for both active substances and for AUC\textsubscript{0-30min} for salmeterol. After comparison of Salmeterol/Fluticasone Hexal and Seretide 50 μg/500 μg, similarity in safety and efficacy has been sufficiently demonstrated.

IV.2 Discussion on the clinical aspects

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.

Clinical efficacy and safety
The Applicant has submitted two supportive 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 Hexal) 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 rest 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 Hexal can be used in subjects from the age of 12 years and older. To conclude, study DPI-1 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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns Salmeterol/Fluticasone Hexal, inhalation powder, pre-dispensed and two different strengths, i.e., 50/250 μg and 50/500 μg. During the procedure, the Applicant withdrew the strength 50/250 μg.

The application for Salmeterol/Fluticasone Hexal 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.
Bioequivalence was demonstrated for Salmeterol/fluticasone Hexal 50 μg/500 μg regarding fluticasone AUC and Cmax and salmeterol AUC, Cmax and AUC_{0-30 min} in study PWDI-7 (without charcoal blockade). Hence, similarity in safety and efficacy for both fluticasone and salmeterol can be concluded based on PK-data.

The Applicant has submitted two supportive clinical studies, Study 2006-56-DPI-1 and VR315/1/001 (Flow rate study Inamed) to this application. The study 2006-56-DPI-1 was a 12-week, randomized, double-blind, double-dummy, parallel group study in adolescent and adult patients with moderate-to-severe persistent asthma (n=555). 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. However, in the study a dose response could not be shown and hence DPI-1 cannot be considered to be a pivotal clinical study on which the therapeutic equivalence can be based on. The data from the flow rate profile study VR315/1/001 support the use of healthy volunteers in the conducted PK studies. A sufficient number of adolescents have been included in the 2006-56-DPI-1 study. Thus, if therapeutic equivalence can be demonstrated with the use of pharmacokinetic data it is considered acceptable that Salmeterol/Fluticasone Hexal can be used in subjects from the age of 12 years and older.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Conclusion
The risk/benefit ratio is considered positive and Salmeterol/Fluticasone Hexal, inhalation powder, pre-dispensed, 50 microgram/500 microgram/dose is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Salmeterol/Fluticasone Hexal, inhalation powder, pre-dispensed, 50 microgram/500 microgram/dose, was successfully finalised on 2013-12-05.
Public Assessment Report – Update

<table>
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<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>
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</table>

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