LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Roadasan Forspiro
(salmeterol, fluticasone propionate)

SE/H/1448/01-02/DC

This module reflects the scientific discussion for the approval of Roadasan Forspiro. The procedure was finalised on 2015-09-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Roadasan Forspiro, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose and 50 microgram/500 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 PL as concerned member state (CMS).

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.

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

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

Table 1. Study package overview and regulatory guidance

Study ID (Study type)	Dose	Assessment of equivalence (safety/efficacy) via:	Ref. to guidance/other pertinent information
Pivotal studies			
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 BE efficacy SX see also PWDI-9; same dose of SX as in PWDI-7	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/604/96 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 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.

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.2 Pharmacokinetics

The application for Roadasan Forspiro concerns two strengths: 50µg/250 µg and 50 µg/500 µg. To support this application with respect to clinical aspects, the Applicant has submitted three pharmacokinetic studies; with and without charcoal blockade (studies PWDI-7, -9 and -17). All studies were single-dose, crossover bioequivalence studies conducted in healthy volunteers. In general, the design of the studies was adequate.

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.

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.

Regarding the 50 µg/500 µg strength:
Bioequivalence between Roadasan Forspiro, 50 µg/500 µg and Seretide was evaluated in study PWDI-7. The test drugs were administered without the administration of active charcoal and hence total systemic exposure was evaluated. The study could therefore be used in the safety evaluation of both salmeterol and fluticasone. Given the low oral bioavailability of fluticasone, the study could also be used as support of similar efficacy of fluticasone. An additional post-hoc analysis of $AUC_{0\text{-}30\ min}$ for salmeterol was also 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. Bioequivalence was demonstrated for AUC and Cmax for both active substances and for $AUC_{0\text{-}30min}$ for salmeterol.

Conclusion: After comparison of Roadasan Forspiro and Seretide 50 µg/500 µg, similarity in safety and efficacy has been sufficiently demonstrated.

Regarding the 50 µg/250 µg strength:
Bioequivalence between Roadasan Forspiro 50 µg/250 µg and Seretide was evaluated in study PWDI-9 (with charcoal blockade) and PWDI-17 (without charcoal blockade).

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 Roadasan Forspiro compared to Seretide. With respect to safety a lower Cmax is not a disadvantage and it could be concluded that safety of salmeterol has been sufficiently demonstrated.

For **fluticasone** bioequivalence regarding AUC was demonstrated, but not regarding Cmax in study PWDI-9. Cmax was 29% lower for the test compared to the reference product. According to the Applicant there is a high variability of FPD for the reference product, both batch to batch variability and within a batch during shelf-life (aging), making it difficult to demonstrate bioequivalence. Therefore, an additional study (PWDI-17) was conducted where it was pre-specified that the pharmacokinetic results should be corrected for FPD.

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.

Conclusion: After comparison of Roadasan Forspiro and Seretide 50 µg/250 µg, similarity in safety and efficacy has been sufficiently shown.

Overall pharmacokinetic conclusion
After comparison of Roadasan Forspiro and Seretide 50 µg/500 µg, similar efficacy and safety regarding both salmeterol and fluticasone has been sufficiently shown.

After comparison of Roadasan Forspiro and Seretide 50 µg/250 µg, similar efficacy and safety regarding both salmeterol and fluticasone has been sufficiently shown.

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 (Roadasan Forspiro) 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 10-12 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. The data is based on very few subjects and should be interpreted with caution but nevertheless the applicant withdrew the claim for adolescents on request from the CMS.

To conclude, study DPI-1 cannot be considered to be a pivotal clinical study on which the therapeutic equivalence is based on. The applicant decided to withdraw the claim for adolescents.

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

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

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, predispensed, 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 Roadasan Forspiro, inhalation powder, pre-dispensed and two different strengths, i.e., 50/250 µg and 50/500 µg.

The application for Roadasan Forspiro 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.

Regarding the 50 µg/500 µg strength, bioequivalence was demonstrated for fluticasone AUC and Cmax and salmeterol AUC, Cmax and $AUC_{0\text{-}30\ min}$ 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.

Regarding the 50 µg/250 µg strength, bioequivalence was evaluated in study PWDI-9 (with active charcoal) and study PWDI-17 (without active charcoal). For salmeterol efficacy was shown to be similar and safety not worse for Roadasan Forspiro compared to Seretide. For fluticasone bioequivalence could be demonstrated after an IVIVC had been established and the PK-data were normalised to reflect a representative batch. Hence, similarity in efficacy and safety of fluticasone 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, the study design suffers from several shortcomings and in thus found non-conclusive. The data from the flow rate profile study VR315/1/001 support the use of healthy volunteers in the conducted PK studies.

Conclusion
To conclude, the risk/benefit ratio is considered positive and Roadasan Forspiro, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose 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 Roadasan Forspiro, inhalation powder, pre-dispensed, 50 microgram/250 microgram/dose and 50 microgram/500 microgram/dose, was positively finalised on 2015-09-29.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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