COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

AirFluSal Forspiro 50/500 microgram/dose, inhalation powder, pre-dispensed

(salmeterol xinafoate/fluticasone propionate)

NL/H/5447/001/DC

Date: 19 August 2021

This module reflects the scientific discussion for the approval of AirFluSal Forspiro 50/500 microgram/dose, inhalation powder, pre-dispensed. The procedure was finalised at 3 August 2015 in Sweden. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for AirFluSal Forspiro 50/500 microgram/dose, inhalation powder, pre-dispensed, from Sandoz B.V.

The product is indicated for:
Asthma
Casorol Forspiro is indicated in the regular treatment of asthma where use of a combination product (long-acting β_2 and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β2 agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist.

Chronic Obstructive Pulmonary Disease (COPD)
Casorol Forspiro is indicated for the symptomatic treatment of patients with COPD, with a FEV_1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product 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 member state originally was Sweden with the Netherlands as concerned member state (CMS). On 22 June 2021 a RMS transfer made the Netherlands the new RMS.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, hybrid application.

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

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.

Note: Study PWDI-9 and PWDI-17 are 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.

IV.2 Pharmacokinetics

Bioequivalence between Casorol Forspiro 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 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 AUC0-30 min for salmeterol was also suggested as a measure of pulmonary deposition in support of salmeterol efficacy. This is acceptable, given the very fast absorption of salmeterol, with maximal plasma concentrations reached after 2-5 min after oral inhalation.

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. To extrapolate results from a pharmacokinetic 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 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. The overall study design is found adequate.

As shown in the tables below bioequivalence was demonstrated for AUC and Cmax for both active substances and also for AUC0-30min 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.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	328.57 ± 109.00	297.50 ± 111.29	0.06 ± 0.02
Reference	282.11 ± 90.83	265.69 ± 84.21	0.06 ± 0.04
*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_{max}) after oral inhalation of 2x 50 µg/500 µg salmeterol/fluticasone n=59.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	1083.11 ± 311.76	148.03 ± 45.16	1.66 ± 1.12
Reference	1166.84 ± 260.88	176.53 ± 49.99	1.40 ± 0.94
*Ratio (90% CI)	0.9129 (0.8791-0.9479)	0.8340 (0.8022-0.8671)	-

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 4: Bioequivalence results for salmeterol $AUC_{0-30\ min}$. Study PWDI-7.

AUC 0-30min	Point estimator	Confidence intervals
N subjects = 59	118.67%*	114.40% - 123.09%*
N subjects = 61	119.34*	115.12% - 123.71%*

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 C_{max} for both active substances and for $AUC_{0-30min}$ for salmeterol. After comparison of Casorol Forspiro and Seretide 50 µg/500 µg, similarity in safety and efficacy can be concluded.

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 (Casorol 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 10-14 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. However, the data is based on very few subjects and should be interpreted with caution. During the procedure the indication was changed to encompass adults only.

To conclude, study DPI-1 cannot be considered to be a pivotal clinical study on which the therapeutic equivalence is based on. Nevertheless, this is acceptable as pharmacokinetic data are regarded sufficient to allow conclusion on clinical efficacy and safety.

IV.5 Risk Management Plan

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 Casorol Forspiro, inhalation powder, pre-dispensed, 50/500 µg.

The application for Casorol 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.

Bioequivalence was demonstrated for Casorol Forspiro 50 µg/500 µg regarding fluticasone AUC and C_{max} and salmeterol AUC, C_{max} 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.

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 Casorol Forspiro, inhalation powder, pre-dispensed, 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 Casorol Forspiro, inhalation powder, pre-dispensed, 50 microgram/500 microgram/dose, was positively finalised on 3 August 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse