LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Salmeterol/Flutikason Jacobsen
(salmeterol xinafoate, fluticasone propionate)

Asp no: 2014-0923

This module reflects the scientific discussion for the approval of Salmeterol/Flutikason Jacobsen. The procedure was finalised on 2015-07-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Salmeterol/Flutikason Jacobsen, 50 µg/500 µg/dose, inhalation powder, pre-dispensed, is a hybrid application (change in pharmaceutical form, bioequivalence cannot be demonstrated through bioavailability studies) made according to Article 10(3) of Directive 2001/83/EC. The applicant, Jacobsen Pharma A/S, applies for a marketing authorisation in Sweden through the National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Seretide Diskus forte, 50 µg/500 µg/dose, inhalation powder, pre-dispensed (SE/H/169/03) authorised in Sweden since 1998, with GlaxoSmithKline AB as marketing authorisation holder.

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 substance has been adequately proven and its physico-chemical properties are sufficiently described.

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

The drug substance specification includes 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

According to the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009), a step-wise approach should be considered when demonstrating therapeutic equivalence for an orally inhaled product. 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 the current application, equivalence was not demonstrated based on pharmaceutical data alone and the demonstration of therapeutic equivalence is mainly based on pharmacokinetic data. In addition one study evaluating the inspiratory profiles and two pharmacodynamic safety studies have been performed.

IV.1 Pharmacokinetics

The demonstration of therapeutic equivalence is mainly based on pharmacokinetic data. 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.

Study SIT001-09 (with and without charcoal) is pivotal for the application. Pharmacokinetic data was also obtained in the pharmacodynamic safety studies (SIT001-03 and SIT001-15).

Pivotal bioequivalence study (SIT001-09)
This was a randomized, open-label, single dose, 4-period crossover design with four treatment arms (T: test, R: reference, TC: test + charcoal, RC: reference + charcoal) conducted in 40 healthy volunteers. The respective treatment was administered after an overnight fast in the morning of Day 1 of each period with or without activated charcoal according to the assigned treatment sequence. Blood samples were collected pre-dose and up to 16 and 48 hours post-dose for salmeterol and fluticasone respectively. The study design is considered acceptable. Plasma concentrations of salmeterol and fluticasone were determined with a validated HPLC/MS/MS method.

The results are presented below.
Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fluticasone without active charcoal, n=40.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**3453 ± 902**	**378 ± 115**	**0.53 0.20-2.07**
Reference	**3877 ± 1241**	**352 ± 110**	**1.03 0.20-6.03**

***Ratio (90% CI)**	**91.42 (84.84-98.50)**	**107.95 (100.09-116.42)**	**-**

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 2: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fluticasone with active charcoal, n=40.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**3413 ± 827**	**366 ± 108**	**1.03 0.20-4.05**
Reference	**3765 ± 1176**	**354 ± 104**	**2.03 0.37-4.05**
***Ratio (90% CI)**	**92.66 (85.99-99.84)**	**103.48 (95.95-111.60)**	**-**

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: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for salmeterol without active charcoal, n=40.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**773 ± 280**	**476 ± 168**	**0.08 0.07-0.13**
Reference	**899 ± 395**	**546 ± 231**	**0.08 0.07-0.28**
***Ratio (90% CI)**	**86.86 (81.32-92.78)**	**89.67 (81.36-98.82)**	**-**

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: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for salmeterol with active charcoal, n=40.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**511 ± 166**	**439 ± 154**	**0.08 0.07-0.13**
Reference	**551 ± 146**	**454 ± 160**	**0.08 0.07-0.13**

***Ratio (90% CI)**	**90.99 (85.18-97.19)**	**96.48 (87.54-106.33)**	**-**
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*

For AUC0-t and Cmax the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both fluticasone and salmeterol after administration with and without active charcoal. For salmeterol Tmax (median and range) was similar for the test and the reference product. The slightly shorter median Tmax for fluticasone for the test product is not considered as clinically relevant. Extrapolation of in vivo data using healthy volunteers to a patient population is acceptable given the similarity in flow-rate dependency.

Additional PK-data from safety studies SIT001-03 and SIT001-15
Although bioequivalence was demonstrated in the pivotal bioequivalence study (SIT001-09), pharmacokinetic analysis of fluticasone in the PD-safety studies, showed a higher exposure of the test product compared to the reference.

In the PD-study SIT001-15, only trough concentrations were measured making a complete pharmacokinetic comparison difficult. Although the trough concentrations were higher for the test product compared to the reference it is not possible to draw any firm conclusion from these findings.

In the PD-study SIT001-03, full PK-profiles were obtained at day 4 in each study period.

The same test and reference batches were used in SIT001-09 and SIT001-03. It is however well known that variability in particle-size distribution within a single batch through their storage period can be significant for orally inhaled products. Given that PK is a sensitive tool, such changes may result in failure to show bioequivalence at some occasions, although bioequivalence may be shown at other occasions in studies with the same or different batches of the same product. The data presented by the Applicant indicate a decrease in fluticasone FPD for the reference product during the time period of 6 months between the conductance of SIT001-09 and SIT001-03. This change in FPD over time may be one explanation why bioequivalence was shown in SIT001-09 but not in SIT001-03.

Although between-study comparisons are generally not recommended, it is interesting to compare the PK-results from SIT001-03 and SIT001-09. Both studies were conducted in healthy volunteers, had a similar sample size and used the same bioanalytical method for determination of fluticasone in plasma. If the results are normalised to dose and expected accumulation factor taken into consideration, the test product AUC was rather similar in both studies. For the reference product the AUC was on the other hand significantly lower in SIT001-03 compared to SIT001-09, which is in line with the observation of a decrease in FPD for the reference product. The deviating PK-results in the PK- and PD-studies may thus be at least partly explained by variability in FPD over time for the reference product.
Conclusion: Bioequivalence has been demonstrated in a well-designed single-dose PK-study in accordance with the recommendations in the OIP-guideline.

IV.2 Clinical efficacy

Conclusion of clinical efficacy was based on bioequivalence and on one flow rate study for acquiring inspiratory profiles for the new powder inhaler (DPI) device PulmoJet as compared to the established Diskus

Flow rate study (SIT001-06)
This was a multicenter, randomized, open-label, intra-subject/patient crossover study for acquiring inspiratory profiles with PulmoJet, Diskus dry powder inhaler (DPI) devices in healthy adult subjects, children with asthma and adult patients with moderate to severe asthma and adult patients with moderate to very severe chronic obstructive pulmonary disease (COPD).

The primary objective was to determine the peak inspiratory flow rates (PIF) generated through the respective devices and to show that patients representative of the anticipated target populations are able to attain a sufficient flow rate to release the trigger mechanism of PulmoJet.

Safety variables included physical examination, vital signs measurement, inspiratory and expiratory lung function variables, documentation of AEs.

The study population included subjects from a broad age range (6-79 years) with different degrees of airway obstruction (FEV1 % predicted, 52-111%). The population is appropriate to cover the objectives of the study.

Results
A total of 124 subjects (male and female) were enrolled:
- Healthy adult subjects (N=20), aged 19-70 years
- Children with asthma (N=20), aged 6-12 years
- Adult patients with moderate to severe persistent asthma (N=41), aged 26-79 years
- Adult patients with moderate to very severe COPD (N=43), aged 49-77 years

The lowest PIF rate was approximately 42 L/min which is higher than the 20 L/min required for the achievement of the trigger threshold of the PulmoJet. Thus it can be concluded that PulmoJet works independent of the FEV1 of the patients within the range tested. The flow rates obtained by the Diskus were consistently higher than that of the PulmoJet. No subject was excluded because he/she was unable to properly handle the PulmoJet inhaler. The secondary endpoints showed a pattern supportive of the primary endpoint.

IV.3 Clinical safety

Two studies documenting the level of cortisol suppression were presented. These are regarded as supportive as conclusion on clinical safety is claimed to be based the pivotal bioequivalence study.

Study SIT001-03
A comparative study on the suppressive hypothalamic-pituitary-adrenal (HPA) axis activity of two salmeterol / fluticasone (SX-FP) fixed combinational dry powder inhaler (DPI) products in healthy adult subjects - A single-centre, randomized, double-blind, double-dummy, 4- period, 4-day repeated dose crossover study with baseline evaluation comparing two strengths (i.e. 50/100 µg and 50/500 µg) SX-FP PulmoJet® and Seretide Diskus® combinational products.

The study was conducted in 40 health volunteers over 4 days. The primary endpoint was to compare the effects of 4-day BID repeat-dose treatment with the 50/500 µg strength of SAL-FP PulmoJet®) with the respective nominal strength of the European reference product (Seretide Diskus® forte) on the integrated area under the curve (AUC) of 24-hour plasma cortisol profiles. Secondary parameters were:

- to compare the effects of 4-day BID repeat-dose treatment with the 50/100 µg strength of SAL-FP PulmoJet® with the respective nominal strength of the European reference product (Seretide Diskus® mite) on the integrated area under the curve (AUC) of 24-hour plasma cortisol profiles
- to compare the effects of the investigational treatments on Cmax of 24-hour plasma cortisol profiles
- to assess and describe the dose-response of 24-hour plasma cortisol response of the test and reference products, to construct dose-response curves to calculate the relative dose-potencies of the 2 products
- to investigate and compare the steady-state pharmacokinetics of the fluticasone component of the investigational treatments
- to assess and compare the occurrence of paradoxical bronchospasm by determination of FEV1
- to assess and compare the general and local tolerability and safety of the investigational treatments.

For the lower strength, the two formulations performed similarly whereas the test product showed a higher level of effect as determined by the primary endpoint investigated. For the primary pharmacodynamic parameter AUC024h,500 the point estimate for the ratio of test compared with reference for the higher dose strength was calculated as 75.58 % with an affiliated 90% confidence interval of 67.22 – 84.99 %. Thus, the lower limit of the one-sided 95 % confidence interval was not above the lower margin of non-inferiority acceptance range of 80.00 %. For the lower strength the corresponding figures were 103.68 % (97.57 – 110.18) implying a considerable difference between strengths.

Pharmacokinetic results
In general, the mean curves of fluticasone propionate after multiple dose administration of test and reference for the higher dose strength compared to the lower are different with regard to course and shape with a distinctly later achievement of tmax and a distinct biexponential decline, which is not apparent for lower dose strength during the observed time period. AUCss0-t and Cmaxss were 30% and 43% higher (test vs reference) for the higher strength. The mean curves after administration of the lower strength show a nearly identical course during the observed time period.

Adverse events
Twenty-four (24) out of 40 subjects reported 62 AEs during the study headache being the most prevalent. There were no SAEs reported. The distribution of adverse events was similar between groups. No clinically relevant changes in the laboratory values, FEV1 values, ECG parameters, vital signs and physical parameters related to safety were observed. There were no SAEs reported.

Study SIT001-15
A study on the effect of salmeterol / fluticasone propionate (SAL/FP) fixed combinational dry powder inhaler (DPI) PulmoJet SAL/FP high in comparison to the Seretide Diskus forte combinational product on the suppressive hypothalamic-pituitary-adrenal (HPA) axis activity - A single-center, randomized, double-blind, double-dummy, 3-period, 7-day repeated dose

crossover study on two different doses (50/500 µg bid and 50/100 µg bid) in adult subjects. 83 healthy volunteers were allocated to the study groups.

The primary endpoint was baseline-adjusted (post-baseline) delta-AUC = ((AUC values of 24-hour cortisol levels, after 7 days of bid 50/500 µg treatment with PulmoJet SAL/FP high (Test 1) and Seretide Diskus forte (Reference). In addition Baseline-adjusted (post-baseline) delta-AUC = ((AUCvalues for PulmoJet SAL/FP high dose and low dose was compared to allow assessment of assay sensitivity. Change in (post-baseline) maximum plasma concentration Delta-Cmax bid, BLA values of 24-hour cortisol levels after 7 days of bid 50/500 µg treatment with PulmoJet SAL/FP high dose and Seretide Diskus forte was also investigated together with the pharmacokinetic trough values of fluticasone (morning and evening of Days 5, 6 and 7). The statistical model used for the analysis of the baseline adjusted AUC was an analysis of variance (ANOVA) model.

In terms of the delta-AUC(0-24), the baseline adjusted AUCs represented a mean reduction in cortisol exposure of 44% and 34% for the PulmoJet SAL/FP high dose and Seretide Diskus forte treatments respectively (see table below), and 8% for the PulmoJet SAL/FP low dose. Thus the results recorded in this study was similar to the results obtained in study SIT001-03 with a somewhat lower variability. The main difference between the two studies is the choice of statistical method and acceptance limits for similarity.

Results pharmacokinetics
The FP trough concentrations indicate that for all 3 treatments the concentrations have reached steady state by Day 5 of bid dosing. The trough concentrations were higher for the test product compared to the reference but as data were sparse it is not possible to draw any firm conclusion from these findings.

Adverse events
Totally 127 TEAEs were reported. All reported TEAEs were of mild or moderate severity, with the majority of reported TEAEs being of mild severity. Headache and dysphonia were the most prevalently reported. There were no relevant differences in frequencies between groups. Two cases (pyelonephritis in the test group (high dose) and urticaria in the control group) led to withdrawal of treatment.

Discussion of clinical aspects
Conclusions on clinical efficacy and safety were drawn based on pharmacokinetic bioequivalence (study SIT001-09). In addition, data are provided from two pharmacodynamic studies (SIT001-03 and SIT001-15) intended to support clinical safety for fluticasone. It is noted that the exposure to fluticasone was higher in the test group as compared to the Seretide reference for the high strength in both these studies although data are too sparse to allow firm conclusions in study SIT001-15. The data presented by the Applicant indicate a decrease in fluticasone FPD for the reference product during the time period of 6 months between the conductance of SIT001-09 and SIT001-03 a fact that could at least partly explain the recorded differences in systemic exposure.

In both these studies a difference between the test and reference products is recorded also for the pharmacodynamic evaluation. In the first of the two studies (SIT001-03) an unexpected difference in level of cortisol suppression between test and reference was recorded for the high dose strength whereas similarity was shown for the lower strength. When the applicant planned the second study (SIT001-15) they chose a somewhat different design. The lower strength is only investigated for the test, not for the reference and thus no conclusions on differences in performance between products for each of the strengths could be drawn although

assay sensitivity was accurately shown. Furthermore, the direct comparisons between the studies are hampered by the use of different kinds of statistics. Although in Study SIT001-15 the primary objective was met (i.e. non- inferiority was shown within a pre-set limit for baseline adjusted AUC for cortisol), the results recorded in Study SIT001-15 followed the same pattern as in SIT001-03 as numerically both the exposure and the effect level was higher for test than for reference. The variability was lower than in study SIT001-03 but else the results are similar. Both these studies indicate higher exposure and higher cortisol suppression for test as compared to reference. For study SIT001-03 the difference in cortisol suppression could be at least partly explained by the higher exposure to fluticasone but due to the sparse pharmacokinetic data recorded no corresponding conclusion could be drawn from study SIT001-15. Thus the rational for the recorded difference remains unexplained. Nevertheless, the magnitude of the difference is deemed minor. Published references show that inhaled fluticasone at therapeutic doses influences the HPA-axis with an effect level of the magnitude recorded in study SIT001-15 and with large individual variability. The 11 % higher effect recorded for the test product in relation to Seretide is small in this context, approximately one third of the difference between the two strengths of the test product. There is no guideline support for any specific non-inferiority margin applied in this kind of study but overall the prespecified limit applied by the company is accepted and thus the results from study SIT001-15 does not change or overrules the conclusion drawn from the pivotal pharmacokinetic study.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Salmeterol/Flutikason Jacobsen.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Systemic effects of fluticasone Adrenal suppression Lower respiratory tract infections (pneumonia) Cardiac arrhythmias
Important potential risks	Medication error with Pulmojet device in patients switching from another marketed device and back Off-label use in children below 12 years of age
Missing information	Safety in pregnant and lactating women Safety in children below 12 years of age Safety in patients with hepatic impairment

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.
Summary of the RMP

The RMP is approved

V. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

For this hybrid application, a conclusion on the benefit/risk balance should be based on documented therapeutic similarity between Salmeterol/Flutikason Jacobsen and the reference product Seretide with addition of data to show adequate performance for the PulmoJet device. No such conclusions could be based on pharmaceutical data only as the test product does not fulfil the criteria for similarity based on *in vitro* data as detailed in the OIP guideline (CPMP/EWP/4151/00 Rev.1, 2009). Instead, bioequivalence for both salmeterol and fluticasone was demonstrated in a pivotal pharmacokinetic study with and without charcoal blockade, together with data on flow rate with the new device, indicating similarity in both efficacy and safety.

As supportive information two additional studies where provided, both pharmacodynamic safety studies showing the suppressive hypothalamic-pituitary-adrenal (HPA) axis activity of the fluticasone component. Pharmacokinetic data on fluticasone obtained from one of the supportive pharmacodynamic studies were however inconsistent with the results from the pivotal bioequivalence study showing higher fluticasone exposure for the test product. It is speculated that this may be at least partly be explained by variability in FPD over time for the reference product. In both the pharmacodynamic studies a differences between test and reference was recorded for cortisol suppression but the magnitude of the difference was too small to be deemed of clinical relevance. The latter of the two studies met its primary objective showing a difference of less than 25 %. Thus the benefit/risk balance is found positive based on established therapeutic similarity with the reference product Seretide.
The benefit/risk balance is considered positive.

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

Salmeterol/Flutikason Jacobsen, 50 µg/500 µg/dose, inhalation powder, pre-dispensed was approved in the national procedure on 2015-07-16.

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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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