LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Salmeterol/Flutikason ELC Group
# (salmeterol xinafoate, fluticasone propionate)

# SE/H/2191/02-03/DC

**This module reflects the scientific discussion for the approval of Salmeterol/Flutikason ELC Group. The procedure was finalised on 2023-01-18. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Salmeterol/Flutikason ELC Group, 50 mikrogram/250 mikrogram/dos, 50 mikrogram/500 mikrogram/dos, Inhalation powder, pre-dispensed.

The active substance is fluticasone propionate and salmeterol xinafoate. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Salmeterol/Flutikason ELC Group 50 microgram / 250 microgram/dose; 50 microgram / 500 microgram/dose, Inhalation powder, pre-dispensed, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, CZ, DK, IT, FR, NO, PL, RO, SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Seretide Diskus mite, 50/250 mikrogram/dos, Inhalation powder, pre-dispensed authorised in SE since 1998, with GlaxoSmithKline AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Viani Diskus Mite, 50 microgram / 100 microgram/dose; Viani Diskus 50 microgram / 250 microgram/dose; Viani Forte Diskus 50 microgram / 500 microgram/dose, Inhalation powder, pre-dispensed from DE with GlaxoSmithKline GmbH & Co. KG as marketing authorisation holder.

The strength 50 micrograms/100 micrograms/dos was also part of the initial application, but this strength was withdrawn at day 160 of the procedure.

**Potential similarity with orphan medicinal products**
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

# 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

**Pharmacology/Pharmacokinetics/Toxicology**
Pharmacodynamic, pharmacokinetic and toxicological properties of salmeterol xinafoate / fluticasone propionate are well known. As salmeterol xinafoate / fluticasone propionate is a widely used, well-known active salmeterol xinafoate / fluticasone propionate, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by Dr Anirban Mallik Thakur, B.V.Sc & A.H. (DVM), M.V.Sc and dated 2021.08.06. The report refers 27 publications up to year 2020.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

**Environmental Risk Assessment (ERA)**
Since Salmeterol/Flutikason ELC Group is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Salmeterol/Flutikason ELC Group from a non-clinical point of view.

# IV. CLINICAL ASPECTS

**Pharmacokinetics**
To support the marketing authorisation application the applicant has conducted three pharmacokinetic studies comparing Salmeterol and Fluticasone propionate with the reference product Viani Diskus, without activated charcoal blockade.

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 thus pharmacokinetic studies were performed. Since therapeutic equivalence was not demonstrated using PK data alone for the lowest strength (50 µg/100 µg), pharmacodynamic studies were also performed (see clinical safety below).

Pharmacokinetic properties of the active substance
*Salmeterol*
Salmeterol acts locally in the lung. There are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/mL or less) achieved after inhaled

dosing.

*Fluticasone propionate*
Absorption: The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5 to 11% of the nominal dose depending on the inhalation device used. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and presystemic metabolism, resulting in oral availability of less than 1 %.

Linearity: There is a linear increase in systemic exposure with increasing inhaled dose.

Elimination: The terminal half-life is approximately 8 hours.

Study 18-05-115
*Methods*
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Salmeterol and Fluticasone propionate, 50 µg/100 µg, inhalation powder with Viani Mite Diskus, 50 µg/100 µg, inhalation powder under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of salmeterol and fluticasone propionate were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-t,}$ $AUC_{0-30\ min}$ and $C_{max}$. The study was conducted between 2018-12-05 and 2018-12-14.

*Results*
The results from the pharmacokinetic and statistical analysis are presented in tables below.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for fluticasone propionate, n=33.**

| Treatment | $AUC_{0-t}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **119.77 ± 61.32** | **23.47 ± 9.82** | **0.33 (0.10-1.25)** |
| **Reference** | **87.69 ± 48.19** | **16.90 ± 5.94** | **0.50 (0.13-1.50)** |
| ***Ratio (90% CI)** | **143.02 (128.11-159.66)** | **169.78 (156.98-183.63)** | **-** |

**$AUC_{0-t}$** 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 salmeterol, n=34.**

| Treatment | $AUC_{0-t}$ pg*h/ml | $AUC_{0-30\ min}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test** | **261.15 ± 129.33** | **23.20 ± 13.27** | **82.00 ± 59.61** | **0.10 (0.07-1.50)** |
| **Reference** | **228.19 ± 121.96** | **17.93 ± 9.86** | **63.22 ± 42.28** | **0.10 (0.07-5.00)** |
| ***Ratio (90% CI)** | **116.93 (109.65-124.68)** | **127.60 (116.51-139.74)** | **125.95 (113.15-140.20)** | **-** |

| | |
|---|---|
| $AUC_{0-t}$ | 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 fluticasone propionate, for $AUC_{0-t}$ and $C_{max}$ the 90 % confidence interval for the ratio of the test and reference products did not fall within the conventional acceptance range of 80.00-125.00 %. For salmeterol, for $AUC_{0-t}$ the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %, however not for $AUC_{0-30\ min}$ and $C_{max}$. $T_{max}$ was similar for test and reference product.

Study 18-09-191

*Methods*

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Salmeterol and Fluticasone propionate, 50 µg/250 µg, inhalation powder with Viani Diskus, 50 µg/250 µg, inhalation powder under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of salmeterol and fluticasone propionate were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-t,}$ $AUC_{0-30\ min}$ and $C_{max}$. The study was conducted between 2019-06-28 and 2019-07-14.

*Results*

The results from the pharmacokinetic and statistical analysis are presented in tables below.

**Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for fluticasone propionate, n=33.**

| Treatment | $AUC_{0-t}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **289.12 ± 120.12** | **51.26 ± 22.47** | **0.67 (0.17-1.52)** |
| **Reference** | **283.41 ± 138.25** | **48.85 ± 22.67** | **0.67 (0.17-1.50)** |
| ***Ratio (90% CI)** | **105.39 (95.12-116.76)** | **105.72 (94.85-117.85)** | **-** |

| | |
|---|---|
| $AUC_{0-t}$ | 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, n=33.**

| Treatment | $AUC_{0-t}$ pg*h/ml | $AUC_{0-30\ min}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test** | **287.00 ± 91.91** | **27.86 ± 13.04** | **89.92 ± 52.55** | **0.08 (0.05-1.50)** |
| **Reference** | **272.49 ± 96.78** | **27.76 ± 14.06** | **97.58 ± 65.00** | **0.08 (0.05-0.83)** |
| ***Ratio (90% CI)** | **105.56 (98.68-112.93)** | **102.41 (91.28-114.90)** | **97.92 (84.92-112.90)** | **-** |

| | |
|---|---|
| $AUC_{0-t}$ | 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 fluticasone propionate, for $AUC_{0-t}$ and $C_{max}$ 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 salmeterol, for $AUC_{0-t}$, $AUC_{0-30\ min}$ and $C_{max}$ the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %. $T_{max}$ was similar for test and reference product.

Study 19-09-079

*Methods*

This was a single-dose, two-way crossover study conducted in 150 healthy volunteers, comparing Salmeterol and Fluticasone propionate, 50 µg/500 µg, inhalation powder with Viani Diskus Forte, 50 µg/500 µg, inhalation powder under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of salmeterol and fluticasone propionate were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-t,}$ $AUC_{0-30\ min}$ and $C_{max}$. The study was conducted between 2020-08-12 and 2020-09-26.

*Results*

The results from the pharmacokinetic and statistical analysis are presented in tables below.

**Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for fluticasone propionate, n=142.**

| Treatment | $AUC_{0-t}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **579.86 ± 298.51** | **72.37 ± 28.80** | **0.83 (0.33-3.02)** |
| **Reference** | **487.16 ± 254.44** | **64.28 ± 25.45** | **0.83 (0.33-3.00)** |
| ***Ratio (90% CI)** | **117.45 (111.34-123.89)** | **111.46 (106.15-117.04)** | **-** |

| | |
|---|---|
| $AUC_{0-t}$ | 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 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for salmeterol, n=142.**

| Treatment | $AUC_{0-t}$ pg*h/ml | $AUC_{0-30\ min}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test** | **291.77 ± 94.04** | **29.19 ± 12.25** | **94.26 ± 51.65** | **0.08 (0.05-1.50)** |
| **Reference** | **260.42 ± 95.49** | **25.20 ± 11.37** | **82.76 ± 48.57** | **0.08 (0.05-1.50)** |
| ***Ratio (90% CI)** | **113.92 (109.55-118.46)** | **115.80 (110.18-121.70)** | **114.18 (107.46-122.33)** | **-** |

$AUC_{0-t}$ 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 fluticasone propionate, for $AUC_{0-t}$ and $C_{max}$ 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 salmeterol, for $AUC_{0-t}$, $AUC_{0-30\ min}$ and $C_{max}$ the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %. $T_{max}$ was similar for test and reference product.

Discussion and overall conclusion

The pharmacokinetic studies were performed without activated charcoal blockade. For fluticasone, the contribution of intestinal absorption to systemic exposure is negligible, and thus a study without activated charcoal can be used for both efficacy and safety comparisons. For salmeterol, the contribution of intestinal absorption to systemic exposure is not negligible but the absorption of the drug in the lung is very quick. Thus, the use of $AUC_{0-30\ min}$ as a surrogate for efficacy in a study without activated charcoal can be accepted.

The batches of test and reference product should be representative for the intended product and the reference product on the market. This has been sufficiently demonstrated. Extrapolating the results from healthy volunteers to patients is acceptable since the test and reference products have similar flow rate dependency (see Quality AR). A PIFR study has also been performed (See Performance of the device below).

The bioequivalence studies and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and OIP Guideline (CPMP/EWP/4151/00 Rev. 1).

For study 18-05-115, the test product demonstrated higher bioavailability. Therefore, the applicant conducted additional pharmacodynamic safety studies. Additionally, the applicant submitted several justifications for equivalent efficacy (See Clinical efficacy below).

For study 18-09-191: For subject 04, reanalysed data was used for the pharmacokinetic analysis although batch acceptance criteria were fulfilled in the original analysis. At Day 106, the applicant provided updated pharmacokinetic and statistical analysis using original values for subject 04. The primary parameters, $C_{max,}$ $AUC_{0-t}$ and $AUC_{0-30min}$ was within the conventional acceptance range of 80.00-125.00 %. Thus, the conclusion that therapeutic equivalence was shown for 50 µg/250 µg strength remains unchanged.

Thus, for 50 µg/500 µg and 50 µg/250 µg strength, therapeutic equivalence between Salmeterol and Fluticasone propionate and Viani Diskus has been sufficiently demonstrated based on pharmacokinetic data.

For 50 µg/100 µg strength, therapeutic equivalence between Salmeterol and Fluticasone propionate and Viani Diskus has not been indisputably shown based on pharmacokinetic data as discussed below.

**Pharmacodynamics**
The pharmacodynamic properties of the two included substances are well known and not further investigated for the product under application.

However, therapeutic equivalence was not established by means of pharmacokinetics for the lowest strength (50 µg/100 µg) as the systemic exposure was found higher for the test product as compared to the reference. To ensure that this higher exposure does not translate into any safety issues, two pharmacodynamic model studies were conducted (studies 19-01-011 and 19-02-012, targeting each of the active components). In addition, a PIF-study was conducted.

**Clinical efficacy**
No data was provided as the applicant based their assumption of therapeutic equivalence on pharmacokinetic data. Equivalent exposure for the lowest strength could nevertheless not be confirmed (see pharmacokinetics above) and the applicant provided a justification for why non-inferiority could be confirmed with regard to efficacy (see discussion section below).

**Clinical safety**
**Study 19-01-011** was a randomised, double-blind, double-dummy, three treatment, three period, 7-days repeated-dose crossover, pharmacodynamic safety study on the effect of test product, Salmeterol/Fluticasone propionate 50 mcg/100 mcg inhalation powder administered via the dry powder inhaler device of Cipla Ltd., India (Batch No.: ID73509) in comparison to the reference product, Viani® Mite Diskus® (salmeterol and fluticasone propionate 50 mcg/100 mcg) by GlaxoSmithKline (Lot No.: JR8M), and Viani® Mite Diskus® (salmeterol and fluticasone propionate 50 mcg/500 mcg) by GlaxoSmithKline (Lot No.: LB4D) and placebo (matching the test product (ID74215) and reference product 1 (870-088)) on suppressive hypothalamic-pituitary-adrenal (HPA) axis activity in healthy adult human subjects. The study included 96 healthy volunteers.
The primary endpoint was mean percent change from baseline to end of treatment in 24-hour plasma cortisol AUC0-24 for the test product vs the low dose (50µg/100 µg) of the reference product. The corresponding comparison with the higher dose (50µg/500 µg) was a secondary objective together with Cmax over 24-hour plasma cortisol. Non-inferiority for the primary endpoint (MPCS) was to be concluded for T vs R1 comparison if the upper limit of two-sided 90% confidence interval less than the non-inferiority margin of 25%. Assay sensitivity was concluded if significant differences was seen between the two strengths of the reference product, and between the test product and the higher dose of the reference product.
The impact on the HPA-axis was found minimal as the reduction in AUC for cortisol was only -7.72 % and -6.59 % for test and reference respectively. The difference between formulations was -1.14 % (09 % CI: -6.69 - 4.42). The dose response comparison between R1and R2 was not statistically significant unless an outlier was excluded.

**Study 19-02-012** was randomised, double blind, placebo controlled, five period crossover study to compare the systemic pharmacodynamic effects in 73 healthy adult male human subjects of a lower dose (150 mcg/300 mcg) and a higher dose (300 mcg/600 mcg) of salmeterol/fluticasone propionate 50 mcg/100 mcg inhalation powder administered via the dry powder inhaler device (Cipla Ltd., India). The objective was to show similarity for safety warranted as pharmacokinetic data indicated higher systemic exposure for the test product relative reference.
For each subject, 12 lead ECG, blood pressure measurement, blood collection for assay of serum potassium & plasma glucose and tremor assessment were carried out. The primary endpoint was heart rate AUC (0-4 hrs) which was assessed for all doses. In statistical analysis, Analysis of Covariance (ANCOVA) was carried out using mixed effects model fitted with sequence, treatment and period as fixed effects, baseline as covariate and subject (sequence) as a random effect for the primary endpoint AUC (0-4 hrs). Treatment differences between test and reference formulation for lower dose and higher dose was calculated by the difference between the least square means and was determined by

95% confidence intervals using a pooled estimate of variance.
The increase in hearth rate was 7.12 bpm and 6.69 bpm (for test and reference respectively for the lower dose) i.e. a difference of 0.43 (90 % CI: -0.64 – 1.5). The corresponding data for the higher dose was 10.8 bpm and 11.1 bpm (difference 0.22 bpm with 90% CI: -0.29 – 0.85).

**Performance of the device**
*PIFR study (CRD/17)* was a randomized, open-label, two-way crossover, multicentre study to assess and compare the inspiratory flow profiles generated through the medication free CIPLA DPI (investigational medical device) and the Seretide Diskus (comparator) in healthy adult subjects, adult patients with moderate to severe asthma, adult patients with moderate to severe COPD and children with asthma including 120 subjects. Six groups of individuals divided based on their medical background were generated and compared.
The objective of the study was to measure PIFR through medication free (contained empty blisters without the active drug or placebo) devices. Test and reference devices were assessed by generating the PIFR data in all subjects (COPD, asthma of different severity including children) who are likely to use the drug product with these devices. PIFR (L/min) generated through the respective DPIs was measured in the study. Subjects were recruited and allocated to groups based on disease severity without considering their inhalatory capacity (i.e. without considering FIV1). Therefore, it remains uncertain whether the included subjects covered the whole range of possible PIFRs. There are adult healthy volunteers and mild asthmatics recruited and thus there are no concerns with regard to the higher part of the range. The lower part of the range it is more uncertain but as children were included, the range of inhalatory capacities can be regarded as covered considering that children have small lungs and thus naturally low FIV1.
Overall, the assessment of the PIFR in ITT population demonstrates that PIFR values generated by the participants using test device are slightly higher than those generated with the reference across all the study populations. The differences between products are nevertheless small and not deemed clinically relevant.

**Discussion on clinical aspects**
Salmeterol/Flutikason ELC Group is presented with three different strengths of fluticasone but for the lowest of these (100µg/50µg) pharmacokinetic data indicated a somewhat higher exposure to both fluticasone and salmeterol. This is deemed acceptable from an efficacy perspective as higher exposure would not translate into lower efficacy provided that the measurements represent the true exposure at active site. In this specific case non-inferiority is shown for relevant endpoints for both salmeterol (AUC0-30min and Cmax) and fluticasone (AUC0-t and Cmax) and these are increased in a similar manner as the ratio between AUC and Cmax is similar. There are no statistics performed confirming similarity which is acceptable considering that there are no established acceptance criteria for difference in ratio and the superiority of test vs control is prominent and consistent. In addition, median Tmax occur at the same (salmeterol) or adjacent (fluticasone) timepoints further confirming similarity of the shape of the curves let be at higher magnitude for the test product. Thus, data do not indicate a difference in deposition pattern within the lung. Although it can be concluded that the test product is non-inferior with regard to efficacy, it remains uncertain whether higher exposure could translate into a clinically meaningful difference in effect for some individuals. The applicant has not made any claims for better effect (which is acknowledged) but there remains an open issue on how to express in the PI (if at all) the fact that non-inferiority rather than equivalence has been shown. Also, this fact could have impact on national decisions on exchangeability. This issue is nevertheless not pursued as this lowest strength 50 mikrogram/100 mikrogram/dos was withdrawn since major objection remained on glucocorticoid safety.

The applicant has conducted two pharmacodynamic safety studies, designed to address safety concerns one for each of the two substances:

Study 19-01-011 was a randomised, double-blind, double-dummy, three treatment, three period, 7-days repeated-dose crossover, pharmacodynamic safety study on suppressive hypothalamic-pituitary-adrenal (HPA) axis activity in healthy adult human subjects. The allocated subjects constitute a

homogenous group with regard to age, sex etc which is appropriate to reduce variability. Crucial to distinguish possible differences between products is to minimise variability caused by the circadic rhythm and else variability is behaviour between periods. Subjects should be kept in-house on assessment dates and instructed to act in a similar manner. The description of instructions to subjects on assessment days in the study report is in this case sparse (only details on administration instructions is given) and thus it is difficult to conclude on whether variability was reduced to the extent possible. The treatment duration is 7 days which is under steady state conditions but which could still be too short to give maximal impact on the HPA-axis. Moreover, the study is conducted at a quite low dose level. The aim of the study is to constitute a pharmacodynamic model showing similarity between products and to achieve its goals the study must be conducted at a dose level where the dose/effect curve is steep (i.e. where HPA-axis inhibition is in the magnitude of 50 % irrespective of dose). It is acknowledged that the dose to be used must consider study subjects' safety as increase of the dose of the lowest strength would imply an increased exposure to salmeterol. No clear rational was given for the non-inferiority margin (25 %) and the choice of dose level for the comparison with a deviating dose (5 x). Minimal impact on the HPA axis was recorded irrespective of treatment arm.
In summary this study as design is not deemed sensitive to answer to the question whether the systemic safety of fluticasone (irrespective of setting, endpoints and treatment duration) from Salmeterol/Flutikason ELC Group will always be similar or lower than to that of Seretide. This issue is nevertheless resolved as the application for Salmeterol/Flutikason ELC Group, 50 mikrogram/100 mikrogram/dos has been withdrawn.

Study 19-02-012 was a randomised, double blind, placebo controlled, five period crossover study to compare the systemic pharmacodynamic effects of test product, Salmeterol/Fluticasone propionate 50 mcg/100 mcg inhalation powder administered via the dry powder inhaler device of Cipla Ltd., India in comparison to the reference product, Viani® Mite Diskus® in healthy adult male human subjects under fasting conditions. The study included 5 arms, i.e., both test and reference are represented by two dose levels and a placebo control is included. The single dose design is overall deemed appropriate for the purpose and the wash out period is sufficient. Heart rate is a well-established endpoint when evaluating safety for a β2-agonist and AUC0-4 is a robust primary endpoint covering the peak effect following administration. The difference between high dose and low dose is x2 (the lower dose was 150/300 µg and the higher dose 300/600 µg) with is the lowest possible and thus ensure maximum assay sensitivity. The primary endpoint is at the highest dose level where the effect is most prominent which is appropriate. No rational (applicable for this study setting) is presented for the chosen non-inferiority margin (i.e. quite high; 10 bpm).
Overall, the results for the primary endpoint appears convincing. There is a clear difference recorded between placebo, low dose and high dose respectively and test and reference are apparently similar at both dose levels. The high dose level increased heart rate with 10.8 and 11.1 bpm (test and reference respectively) whereas the corresponding figures for the low dose level was 7.1 and 7.0 bpm. However, the applicant has not presented any valid non-inferiority margin as the prespecified figure (10 bpm) is too large to be relevant in this setting. Applying this limit, both the two dose levels and the low dose vs placebo respectively would be regarded similar which is not at all a reasonable acceptance criterion. On request the applicant presented calculations for relative potency and showed similarity within the acceptance criteria 0.67 – 1.50 for the primary endpoint. Thus, it is confirmed that safety (with regard to the salmeterol component) for the 50/100 µg strength is similar to the reference product.

As the device is new to the EU market a PIFR-study was conducted. This latter study confirmed that the device may be emptied by a variety of subjects including children and patients with severe COPD. The PIFR showed similar or slightly higher for the test product as compared to the reference device (Diskus) with consistent results in all investigated groups of subjects. Overall, the test device performed adequately well.

The application covered all age groups for which the reference product is approved. As no data in children has been presented and therapeutic equivalence could not be concluded by means of *in vitro* data, the age limit was set to 12 years of age.

**Overall discussion on therapeutic equivalence**
In line with the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009), a step-wise approach was applied where equivalence could not demonstrated based on pharmaceutical data alone for any of the strength (first step). The two higher strengths showed bioequivalent in a study conducted without charchoal (where $AUC_{0-30min}$ was used as surrogacy for effect for salmeterol which is an acceptable approach for salmeterol; in case of fluticasone charchoal is not needed due to low oral bioavailability). Thus equivalence was confirmed for these strengths by means of pharmacokinetics (second step).

The lowest strength however showed to give higher systemic exposure for test than for reference with 90 % CI for the ratio of: Fluticasone $AUC_{0-t:}$:128.11-159.66; fluticasone $C_{max}$: 156.98-183.63; salmeterol $AUC_{0-t:}$ 109.65-124.68; salmeterol $AUC_{0-30min}$: 116.51-139.74 and salmeterol $C_{max}$: 113.15-140.20. It could be concluded that the exposure was consistently and significantly higher for test vs reference and therefore, the applicant conducted two pharmacodynamic model studies (step 3). Absence of efficacy data was justified as the amount of drug reaching the lungs is higher and the deposition pattern of drug particles within lungs appears similar. Thus non-inferior efficacy could be confirmed. Nevertheless, there remains an open issue on how to express in the PI (if at all) the fact that non-inferiority rather than equivalence has been shown. Also, this fact could have impact on national decisions on exchangeability. This issue is nevertheless not pursued as the application for 50 mikrogram/100 mikrogram/dos has been withdrawn.

Study 19-01-011 conducted with the lowest strength (50/100 µg) aimed at showing that the safety profile for the glucocorticoid effect (fluticasone component) is at least not worse for test than for reference. This study was nevertheless not deemed sensitive to answer to the question whether the systemic safetyof fluticasone (irrespective of setting, endpoints and treatment duration) from Salmeterol/Flutikason ELC Group will always be similar to that of Seretide but the strength was withdrawn.

Study19-02-012 was also conducted with the 50/100 µg strength and aimed at comparing safety profiles for the adrenerigc effect (salmeterol component). The study is adequately designed and conducted using an established model and the results reassuring. Relative potency within the accpetance criteria 0.67 – 1.50 could be confirmed. Thus, similar safety for the salmeterol component for the lowest strength has been established based on pharmacodynamic data.

**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 Devatis.

Safety specification
In response to a question posed the applicant has updated the summary of safety concerns as below.

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Pneumonia in patients with COPD |
| Important potential risks | None identified |
| Missing information | None identified |

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 submitted Risk Management Plan, version 0.1 signed 23-11-2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

# 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 PL was English. Assessment of the User Testing is attached in Appendix I.

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

The quality of the applied drug product, Salmeterol/Flutikason ELC Group is found adequate. There are no objections to approval from a non-clinical and clinical point of view. Therapeutic equivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

# VII. APPROVAL

The decentralised procedure for Salmeterol/Flutikason ELC Group, 50 mikrogram/250 mikrogram/dos, 50 mikrogram/500 mikrogram/dos, Inhalation powder, pre-dispensed was positively finalised on 2023-01-18.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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