CBG MEB

Public Assessment Report

Scientific discussion

Fluticasonpropionaat 125 and 250 microgram/dosis Vincion, pressurised inhalation, suspension

(fluticasone propionate)

NL License RVG: 116004-116005

Date: 16 October 2017

This module reflects the scientific discussion for the approval of Fluticasonpropionaat 125 and 250 microgram/dosis Vincion, pressurised inhalation, suspension. The marketing authorisation was granted on 28 September 2015. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Fluticasonpropionaat 125 and 250 microgram/dosis Vincion, pressurised inhalation, suspension from Vincion BV.

This product is indicated for:
- The prophylactic treatment of bronchial asthma.
- Symptomatic treatment of chronic obstructive pulmonary disease (COPD) with FEV1 <60%.

As addition to a long-acting β2-agonist for the symptomatic treatment of patients with COPD (FEV1 < 60%) of the predicted normal value (pre-bronchodilator) and a history of repeated exacerbations with significant symptoms.

Fluticasonpropionaat Vincion is indicated in adults and not suitable for use in children.

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

This national procedure concerns a hybrid application claiming similarity with the innovator products Flixotide 125 and 250 micrograms per metered dose inhalator CFK-vrij, pressurised inhalation (NL license RVG 16213-4). Flixotide has been registered by GlaxoSmithKline B.V. since 25 January 1994 in the Netherlands trough a national procedure.

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

II. QUALITY ASPECTS

II.1 Introduction

Fluticasonpropionaat Vincion is a white homogeneous suspension.

Every Fluticasonpropionaat Vincion pre-dispensed dose 125 or 250 microgram fluticasone propionate (metered dose). This is equivalent to a delivered dose of 110 or 220 microgram fluticasone propionate.

The suspension is packed in a aluminum container with a suitable metering valve and a polypropylene actuator with dose indicator and fitted with dust cap in a sealed pouch with a desiccant. Each container is filled to deliver 120 metered doses.

The only excipient is norflurane (HFA 134a) as propellant.

II.2 Drug Substance

The active substance fluticasone propionate is an established active substance, described in the Ph.Eur. The active substance is practically insoluble in water, sparingly soluble in methylene chloride, and slightly soluble in alcohol. Polymorphic form I is used. This form is maintained throughout the manufacturing process of the drug product and upon storage. Since the drug product is a pressurized metered dose inhaler, in which the drug substance is present as a suspension, the particle size of the drug substance is critical for the performance of the drug product. The particle size limit was demonstrated to be suitable for the drug product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with or tighter than the Ph. Eur. requirements with the additional parameters as mentioned on the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches.

Quality control of drug substance
The active substance specification is in line with the Ph. Eur., the additional parameters as mentioned on the CEP and additional in-house requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three commercial scale batches stored at 12 months at 25°C/60%RH and 6 months at 40°C/75%RH that justify the proposed re-test of 12 months. The batches were stored in the commercial packaging.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of the excipient is justified and its function is explained. All aspects of the *Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products* and of the *Guideline on the 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* regarding the pharmaceutical equivalence between the test the and reference product have been discussed.

Therapeutical equivalence could not be demonstrated based on solely in-vitro data. Bioequivalence has been investigated with the 250 microgram strength only. The batches used in these studies are acceptable. Results of Cascade impactor in-vitro testing have been provided to justify a biowaiver for the 125 microgram strength. Calculation of correlations and ratios for Fine Particle Mass (FPM) and all individual stages of the Impactor and assessment based on acceptance criteria for correlation and ratio that correspond with ±15% deviations in the 125 strength compared to the 250 strength, demonstrate that the two strengths of the test product are linear for FPM and all individual stages. However, these evaluations do not demonstrate linearity for the reference product for some specific stages (S2, S4, S5 and S7). Yet, as linearity does comply for FPM and the FPM specifications of the reference product described in the innovator product dossier indicate that these two strengths are also linear, linearity is considered confirmed for the reference product as well. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consist of mixing the drug substances with the propellant under stirring and pressure and filling the mixture into the containers. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches of both strengths. The data adequately demonstrated that the drug product can be manufactured in a reproducible way.

Control of excipients
The excipient norflurane complies with an in-house specification. This is acceptable as testing according the Ph Eur monograph is currently impossible due to monograph restrictions. The in-house specification is the currently usual specification and acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, average weight, number of actuations per container, moisture, FPM, microbiological contamination, total can assay, mean delivered dose, delivered dose uniformity, leak test, related substances and particulate matter.
The specifications for FPM have been adequately justified based on the results of the batches used in the pharmacokinetic studies, range observed in the tested reference product batches and the variation in batches of the proposed products. The proposed limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches of both strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full scale batches of both strengths. The batches were stored for 24 months at 25°C/60%RH and 30°/65%RH and 6 months at 40°/65%RH. The batches were stored in the commercial packaging. The only trend observed in the stability studies was a slight increase in water content, however that increase did not provoke any changes in the other parameters of the drug product. The stability results support the accepted shelf-life and storage condition of 2 years, in the outer packing, stored not above 30°C.
An in-use stability study was conducted, covering 4 months. It was adequately demonstrated that the product is stable for 4 months after opening the pouch and stored with and without aluminium sachet.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Fluticasonpropionaat Vincion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

Since Fluticasonpropionaat Vincion is intended for hydric substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.1 Discussion on the non-clinical aspects

This product is a hybrid formulation of Flixotide which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

Fluticasone propionate is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two, one replicate design and one standard, bioequivalence studies, which are discussed below.

IV.1 Pharmacokinetics

The MAH conducted two bioequivalence studies (one study with - and one study without the use of a volumatic spacer) in which the pharmacokinetic profile of the test product Fluticasonpropionaat 250 microgram/dosis Vincion, pressurised inhalation, suspension (Vincíon BV, the Netherlands) is compared with the pharmacokinetic profile of the reference product Flixotide 250 micrograms per metered dose inhalator CFK-vrij, pressurised inhalation (GlaxoSmithKLine B.V., the Netherlands).

The choice of the reference product in the bioequivalence studies is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver was requested for fluticasone propionate 125 microgram inhaler. To support the biowaiver for the 125 microgram strength, dose linearity was demonstrated in vitro for both the test and the reference product of fluticasone propionate across all proposed strengths, i.e. 125 and 250 mcg. The MAH has evaluated the dose proportionality on the FPM and individual stages for the Fluticasone content between the strengths 125 mcg and 250 mcg of the test product and that of the reference product strengths. Based upon the data for correlation coefficient, it can be concluded that dose proportionality exists across the two strengths of test product for FPM as well as individual stages. Therefore, a biowaiver for lower strength (125 mcg) is justified.

Bioequivalence studies

Study I – PRC/CRD/05/11

Design

A single-dose, randomised, open-label, two-treatment, four-way crossover, replicate bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 21-39 years. A single dose of 4 puffs (either test or reference product) containing fluticasone 1000 microgram (4*250 microgram) was inhaled by the subjects in a standing position after an overnight fast of approximately 10 hours. There were 4 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.08, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4, 5, 6, 8, 10, 12, 18, 24 and 36 after administration of the products.

The design of the study is acceptable. As stated in the protocol this study was designed as a replicate study to reduce the intra-subject variability, which is acceptable. The washout period of 14 days at least 10 times of elimination half-life is considered adequate (t1/2, 7-12 hours). No pre-dose levels (four periods) were identified. As the pharmacokinetics of fluticasone is dose proportional and for purposes of obtaining high enough plasma concentrations to determine reliably, the higher dose of 4 puffs (i.e. 1000 microgram) is acceptable. In the SmPC, fluticasone is recommended to be administered 100-1000 microgram twice daily in adults.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

3 subjects withdrew from the study due to personal reasons and one subject due to unacceptable inhaler technique (significant leakage was observed). One subject only completed 3 periods as he did not arrive for the fourth period of the study. It is agreed that this subject should be included in the statistical analysis, as he completed the first 3 treatment periods (R-T-R). Thus, according to the Guidance on the Investigation of Bioequivalence, the demonstration of bioequivalence will be mainly evaluated based on the statistical analysis for 29 subjects.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fluticasone propionate under fasted conditions inhaled without volumatic spacer.

Treatment N=57	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test (N=57)	1810 ± 770	1902 ± 796	224 ± 96	1.0 (0.5 – 3.5)	8.4 ± 2.0
Reference (N=58)	1702 ± 740	1798 ± 762	209 ± 86	1.0 (0.25 – 4.0)	8.6 ± 1.7
***Ratio (90% CI)**	1.05 (0.98 – 1.13)	1.05 (0.98 – 1.13)	1.05 (0.98 – 1.13)	--	--
CV (%)	21.9	21.7	22.9	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Study II - PRC/CRD/02/12

Design
A single-dose, randomised, open-label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 21-41 years. A single dose of 4 puffs (either test or reference product) containing fluticasone 1000 microgram (4*250 microgram) was inhaled by the subjects with the aid of volumatic spacer in a standing position after an overnight fast of approximately 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose at 0.08, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4, 5, 6, 8, 10, 12, 18, 24 and 36 after administration of the products.

The design of the study is acceptable. As stated in the protocol this study was designed as a replicate study to reduce the intra-subject variability, which is acceptable, and the washout period of 14 days at least 10 times of elimination half-life is considered adequate (t1/2, 7-12 hours). No pre-dose levels (four periods) were identified. As the pharmacokinetics of fluticasone is dose proportional and for purposes of obtaining high enough plasma concentrations to determine reliably, the higher dose of 4 puffs (i.e. 1000 microgram) is acceptable. In the SmPC, fluticasone is recommended to be administered 100-1000 microgram twice daily in adults.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Three subjects withdrew from the study due to personal reasons. Therefore, a total of 25 were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fluticasone propionate under fasted conditions inhaled with volumatic spacer.

Treatment N=<X>	AUC_{0-t} pg/ml/h	$AUC_{0-\infty}$ pg/ml/h	C_{max} pg/ml	t_{max} h	$T_{1/2}$ h
Test	7128±2140	7530±2299	657±180	2.0 (0.5 – 4.0)	8.6±1.1
Reference	6898±2111	7253±2195	687±200	1.5 (0.75 – 10.0)	8.6±1.4
***Ratio (90% CI)**	1.04 (0.96 – 1.12)	1.03 (0.96 – 1.12)	0.96 (0.88 – 1.05)	-	-
CV (%)	15.0	15.2	18.1		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

In-transformed values

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Fluticasonpropionaat 250 microgram/dosis Vincion, pressurised inhalation, suspension is considered bioequivalent with Flixotide 250 micrograms per metered dose inhalator CFK-vrij, pressurised inhalation.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

The results of the studies with 250 microgram formulation can be extrapolated to other strength 125 microgram according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

IV.2 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 Fluticasonpropionaat Vincion

- Summary table of safety concerns as approved in RMP

Important identified risks	- Candidiasis of the mouth and throat - Hypersensitivity reactions (including angioedema and anaphylactic reactions) - Systematic effects (including Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, cataract, glaucoma). - Psychiatric reactions (including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in

	children)). - Paradoxical bronchospasm
Important potential risks	- Adrenal suppression - Off-label use in children below 12 years old - Off-label use in COPD
Missing information	- Patients with hepatic impairment - Safety in lactating mothers - Information on children aged 4 to 11 years. - Safety in patients with active or latent infections (including quiescent and active tuberculosis

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Flixotide. No new clinical studies were conducted. Bioequivalence has been demonstrated for both strengths. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Fluticasonpropionaat 125 and 250 microgram/dosis Vincion, pressurised inhalation, suspension have a proven chemical-pharmaceutical quality and are hybrid forms of Flixotide 125 and 250 micrograms per metered dose inhalator CFK-vrij, pressurised inhalation. Flixotide is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence between Fluticasonpropionaat Vincion and Flixotide has been shown to be in compliance with the requirements of European guidance documents.

In the Board meeting of 15 April 2015, the biowaiver for the 125 microgram strength was discussed. After bioequivalence has been demonstrated between the two strengths, all pharmacokinetic issues were considered resolved. In addition, the use of this product in adolescents was discussed. After raising the age limit of the indicating, this issue was also resolved.

The MEB, on the basis of the data submitted, considered that similarity has been demonstrated for Fluticasonpropionaat Vincion with the reference product, and has therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Replacement or addition of a manufacturer responsible for importation and/or batch release; Including batch control/testing	IA	12-11-2015	26-11-2015	Approved	N
Replacement or addition of a site where batch control/testing takes place	IA	12-11-2015	11-01-2016	Approved	N
European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph; Updated certificate from an already approved manufacturer	IA/G	31-01-2017	08-02-2017	Approved	N
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006; Implementation of wording agreed by the competent authority	IB/G	24-04-2017	17-05-2017	Approved	N
Replacement or addition of a site where batch control/testing takes place	IA/G	24-07-2017	24-08-2017	Approved	N