LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Sirkava 18 microgram tiotropium bromide

SE/H/1710/01/DC
2017-0378

This module reflects the scientific discussion for the approval of Sirkava. The procedure was finalised on 2018-09-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Sirkava, 18 µg, inhalation powder, hard capsule, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Ferrer Internacional, S.A. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (all CMS) as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Spiriva 18 microgram, inhalation powder, hard capsule authorised in Netherlands since 2001, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Spiriva 18 microgram, inhalation powder, hard capsule from Spain with Boehringer Ingelheim International GmbH as marketing authorisation holder.

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

IV.1 Pharmacokinetics

Following inhalation, tiotropium bromide has a bioavailability of 19.5% while oral solutions of tiotropium bromide have an absolute bioavailability of 2-3%. Following an inhaled dose of tiotropium bromide maximal plasma concentrations occur at approximately 5-7 minutes. Tiotropium demonstrates linear pharmacokinetics in the therapeutic dose range. Tiotropium bromide is not metabolised to a large extent. 74% of an intravenous dose is excreted in the urine as unchanged substance. Following inhalation the effective half-life was between 27 and 45 hours in COPD patients.

Pharmacokinetic studies aim at demonstrating similar pulmonary deposition and similar total systemic exposure between a hybrid inhalation 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. For some inhaled medicinal products, the contribution of intestinal absorption to systemic exposure is negligible (<5%) and a single dose PK study without charcoal can be used for both efficacy and safety comparisons. According to the Q&A document published by the Pharmacokinetic Working Party, in case the contribution of intestinal absorption to systemic exposure is not negligible but if the absorption of the drug in the lung is very quick (e.g., $t_{max} \leq$ 5 min) and absorption occurs before the contribution of gastrointestinal absorption is significant (e.g., salbutamol/albuterol, salmeterol), $AUC_{0\text{-}30\ min}$ might be acceptable as a surrogate for efficacy and $AUC_{0\text{-}t}$ for safety. Thus, also in this case, one study without active charcoal blockade is sufficient.

The pivotal study was performed without activated charcoal blockade. In a previous pilot study, CFA-193-P, administration was performed with and without activated charcoal. Based on the results of this study, the applicant concluded that the contribution of intestinal absorption to systemic exposure following inhalation was not negligible. However, since tiotropium was quickly absorbed in the lung the applicant suggests using a truncated AUC in a study without activated charcoal as a surrogate for efficacy. The endpoint $AUC_{0\text{-}15\ min}$ was chosen by the applicant as surrogate for efficacy, since later time points would increase the influence of gastrointestinal absorption. See further discussion below.

To support the application, the applicant has submitted one pivotal pharmacokinetic study with the final formulation; study CFA-193-3.

Five pharmacokinetic pilot studies were performed during the development programme in order to optimize the clinical design of the studies and to confirm the parameters influencing the formulation concept as well as to support the selection of the most appropriate form of lactose/active pharmaceutical ingredient size. Based on the results of the first pilot studies, the

formulation was revised and several variants of the formulation were then tested in two parallel PK studies (CFA-193-P4 and CFA-193-P5). The batch with the best results was then selected for the pivotal PK study.

The pivotal pharmacokinetic study CFA-193-3 was a two-treatment, four-period, two-sequence (TRTR and RTRT) single-dose replicate crossover study conducted in 56 healthy volunteers, comparing Tiotropium Bromide, 18µg, inhalation powder, hard capsules with Spiriva, 18µg, inhalation powder, hard capsules under fasting conditions without concomitant administration of activated charcoal. It is considered sufficiently demonstrated that the flow rate dependency is similar for test and reference, and thus extrapolation of the results to the patient population is acceptable. The batches used in the study are representative for the intended product and the reference product on the market. The study was conducted between 24th April and 22nd August 2016. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable and it is agreed that an early partial AUC can be used as surrogate for tiotropium efficacy in a study without activated charcoal. However, the applicant was asked to further justify why $AUC_{0\text{-}15\ min}$ was used as early partial AUC parameter and to submit data also for $AUC_{0\text{-}30\ min}$. The applicant submitted results for $AUC_{0\text{-}30\ min}$, and since the results were within acceptance criteria, this issue was resolved.

Plasma concentrations of tiotropium were determined with an adequately validated LC/MS/MS method. According to the original statistical analysis performed by the applicant, for $AUC_{0\text{-}t}$, $AUC_{0\text{-}15\ min}$ 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% (see table 1). However, recalculation was requested by the RMS, with data for subject 13 included, and the use of a different statistical method was also requested. This did not significantly affect the results, and did not affect the conclusion regarding equivalence (see table 2, which is the relevant statistical analysis for this study).

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for tiotropium, n=106 (53 subjects, 2 administrations each).

Treatment	**$AUC_{0\text{-}t}$** pg*h/ml	**$AUC_{0\text{-}15\ min}$** pg*h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	**27.97±7.67**	**0.91±0.43**	**5.359±2.91**	**0.07 (0.03-2.00)**
Reference	**24.70±7.27**	**0.81±0.39**	**4.799±2.58**	**0.07 (0.03-0.25)**
***Ratio (90% CI)**	**114.60 (108.94-120.55)**	**111.37 (103.42-119.93)**	**112.29 (103.92-121.34)**	**-**

$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 2: Statistical analysis using WinNonLin method A, including subject 13

EMA/618604/2008 Rev. 13 Q&A Method A			
	including subject #13		
	PE	LL	UL
C_{max}	112.95	104.57	122.01
AUC_{0-15}	111.93	103.97	120.51
AUC_{0-30}	113.14	105.67	121.14
AUC_{0-t}	114.88	109.28	120.76
AUC_{0-inf}	101.70	96.53	107.14

Acceptance Criteria: 80.00-125.00

Since the results for C_{max}, $AUC_{0-30min}$ and AUC_{0-t} were within the conventional acceptance range of 80.00-125.00%, therapeutic equivalence between test and reference can be concluded regarding both efficacy and safety. Thus, therapeutic equivalence between test and reference product can be concluded based on pharmacokinetic data.

IV.2 Discussion on the 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 clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Sirkava.

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Cardiac mortality • Blood and lymphatic system disorders • Blood glucose increased • Psychiatric disorders • Syncope • Cardiac disorders (ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure, angina pectoris) • Vascular disorders (aneurysm, hypertension) • Renal failure • Overdose • Medication errors
Missing information	• Treatment of pregnant and/or breastfeeding women • Treatment of children (aged 18 years or younger) • Patients with a recent history of myocardial infraction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure

V. USER CONSULTATION

A bridging report regarding the content was made to the Favynd 18 microgram, inhalation powder, hard capsule NL/H/3136/01/DC. The bridging report submitted by the applicant has been found acceptable.

The bridging for the layout is confirmed to follow the in house style which has been tested for TRINOMIA ES/H/0241/001-003/DC. This is accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

There are no objections to approval of Sirkava from a quality, non-clinical and clinical point of view. Therapeutic equivalence between test and reference product can be concluded based on pharmacokinetic data. The product information is acceptable.
The application is therefore approvable.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 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 Sirkava, 18 μg, inhalation powder, hard capsule was positively finalised on 2018-09-27.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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