LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tiogiva,
(tiotropium bromide)

SE/H/1924/01/DC

This module reflects the scientific discussion for the approval of Tiogiva. The procedure was finalised on 2020-10-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Glenmark Pharmaceuticals Nordic AB has applied for a marketing authorisation for Tiogiva, 18 µg, Inhalation powder, hard capsule. The active substance is tiotropium, a long-acting, specific, muscarinic receptor antagonist.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC 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

Pharmacodynamic, pharmacokinetic and toxicological properties of tiotropium are well known. As tiotropium is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

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

Environmental Risk Assessment (ERA)

Since Tiogiva are intended for substitution with marketed products containing the same active substance, 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 Tiogiva from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tiotropium is a well-known substance used as inhalation in obstructive lung diseases. It is used as maintenance treatment, one dose of 18 µg daily. This application is submitted according to Article 10(3) of Directive 2001/83/EC and the authorisation is based on therapeutic equivalence between test and reference product.

IV.2 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.

To support the application, the applicant has submitted four PK studies (two pilot and two pivotal) and an inspiratory flow characteristic study.

The pilot studies were performed in order to select the formulation and inhaler device to the pivotal pharmacokinetic studies and is not further described. Two pivotal pharmacokinetic studies were performed withot activated charcoal, see summary of these studies below. Two different version of the MRX003-T10 device were used in the two pivotal pharmacokinetic studies. However, the difference between these device versions would be expected to have no effect upon device or formulation performance. When the first pivotal study was initiated it was intended as a sole pivotal study. However, this study did not show therapeutic equivalence and therefore a second pivotal study was conducted.

Pivotal study TIO-H1018/64

Methods

The study was a single centre, open-label, randomised, two-treatment, three-period, three-sequence (TRR, RRT and RTR) crossover semi-replicate study conducted in 69 healthy volunteers under fasting conditions without concomitant administration of activated charcoal. After an overnight fast of at least 10 hours, the dose of two inhaler capsules of approximately 20 mcg tiotropium delivered dose (corresponding to 36 mcg of tiotropium nominal dose) of either test or reference product was administered. Each capsule was inhaled by the subjects twice, thus the required total number of inhalations for the two inhaler capsules were 4 inhalations. The normally recommended dose for the reference product is one capsule to be inhaled once daily, using two inhalations in order to empty the capsule completely. In this study two capsules were administrated in order to get sufficiently high plasma concentrations. This is found acceptable.

Blood-samples were collected pre-dose and at 2 (0.033 hours), 4 (0.067 hours), 6 (0.10 hours), 8 (0.133 hours), 10 (0.167 hours), 12 (0.20 hours), 15 (0.25 hours), 30 (0.50 hours) 45 (0.75 hours) minutes after drug administration and at 1.00, 2.00, 4.00, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, 72.00 hours after drug administration. Plasma concentrations of tiotropium were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-30min}$ and C_{max}. The study was conducted between 11/11/18 and 08/02/19.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for tiotropium, n=68.

Treatment	AUC_{0-t} pg*h/ml	$AUC_{0-30\ min}$ pp*h/ml	C_{max} pp/ml	t_{max} h
Test	**45.29±13.42**	**2.64±1.50**	**10.486±8.53**	**0.10 (0.03-4.00)**
Reference (B-B)	**39.94±11.84**	**2.09±1.14**	**7.652±4.87**	**0.10 (0.03-4.00)**
***Ratio (90% CI)**	**114.06 (110.69-117.52)**	**125.13 (118.77-131.83)**	**130.36 (122.53-138.69)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ 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*

Therapeutic equivalence was demonstrated for AUC_{0-t} but not for $AUC_{0-30min}$ and C_{max} (for both $AUC_{0-30min}$ and C_{max} the upper limit of the 90% CI of the test/reference ratio was above the highest acceptance criteria of 125.00).

The study was performed without activated charcoal blockade. For substances with very quick absorption in the lung (e.g., $t_{max} \leq 5$ min), it is agreed that an early partial AUC can be used as a surrogate for efficacy in a study without activated charcoal. With an early t_{max}, lung absorption will occur before the contribution of gastrointestinal absorption is significant. Even though median t_{max} was 6 minutes in this study (i.e. slightly later than recommended) it is found acceptable to use early partial AUC in this case. As recommended by PKWP Q&A the applicant has used $AUC_{0-30min}$ as partial AUC which is found acceptable.

Pivotal Study TIO-H0319/16

Methods

The study was a single centre, randomised, two-treatment, two-period, two-sequence (TR and RT) crossover single dose study conducted in 48 healthy male volunteers under fasting conditions without concomitant administration of activated charcoal. After an overnight fast of at least 10 hours, two

inhaler capsules of either test or reference product were administrated, each capsule was inhaled by the subjects twice, thus the required total number of inhalations for the two inhaler capsules (=approximately 20 mcg tiotropium delivered dose, 36 mcg tiotropium nominal dose) were 4 inhalations with a 30 second interval from the start of one inhalation to the other, including breath holding as long as comfortable after each inhalation. The normally recommended dose for the reference product is one capsule to be inhaled once daily, using two inhalations in order to empty the capsule completely. In this study two capsules were administrated in order to get sufficiently high plasma concentrations. This is found acceptable.

Blood-samples were collected pre-dose and at 2 (0.033 hours), 4 (0.067 hours), 6 (0.10 hours), 8 (0.133 hours), 10 (0.167 hours), 12 (0.20 hours), 15 (0.25 hours), 30 (0.50 hours) 45 (0.75 hours) minutes after drug administration and at 1.00, 2.00, 4.00, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, 72.00 hours after drug administration. Plasma concentrations of tiotropium were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-30min}$ and C_{max}. The study was conducted between 10/04/19 and 02/07/19.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for tiotropium, n=45

Treatment	AUC_{0-t} pg*h/ml	$AUC_{0-30min}$ p*h/ml	C_{max} pg/ml	t_{max} h
Test	**45.93±14.26**	**2.65±1.31**	**9.612±6.10**	**0.10 (0.03- 0.17)**
Reference	**45.48±15.76**	**2.52±1.25**	**9.080±5.13**	**0.07 (0.03- 0.17)**
***Ratio (90% CI)**	**102.72 (96.85-108.95**	**106.77 (97.78-116.58)**	**106.78 (96.56-118.09)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ 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*

For AUC_{0-t}, $AUC_{0-30min}$ 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%.

The study was performed without activated charcoal blockade. For substances with very quick absorption in the lung (e.g., tmax ≤ 5 min), it is agreed that an early partial AUC can be used as a surrogate for efficacy in a study without activated charcoal. With an early t_{max}, lung absorption will occur before the contribution of gastrointestinal absorption is significant. Even though median t_{max} in this study was 6 minutes and 4.8 minutes for test and reference product respectively (i.e. slightly later than recommended) it is found acceptable to use early partial AUC in this case. As recommended by PKWP Q&A the applicant has used $AUC_{0-30min}$ as partial AUC which is found acceptable.

Discussion and overall conclusion

In this application there is one pivotal pharmacokinetic study that failed to show therapeutic equivalence whereby the other pivotal pharmacokinetic study showed therapeutic equivalence. Different batches of the reference product were used in the two pharmacokinetic studies. Both these batches are considered representative (median± 15%) even though the reference batch used in the failed PK study is just on the limit of acceptance regarding FPD.

The failure to show therapeutic equivalence in the first pivotal PK study could in this case be explained by the reference batch being at the lower end of acceptance regarding FPD. This is further supported by the theory that a lower FPD of the reference product gives lower exposure and thus higher point estimates of Cmax and AUC in the test/reference comparison, which is the case in the failed study. When a median batch of the reference product regarding FPD is used in the second pivotal PK study the point estimates of Cmax and AUC is lowered.

Thus, results of the first pivotal study can be explained by a low FPD of the reference product, and the the second pivotal PK study (with a reference product closer to the median FPD) that show therapeutic equivalence is considered sufficient in order to demonstrate therapeutic equivalence for this application.

IV.3 Pharmacodynamics/Clinical efficacy/Clinical safety

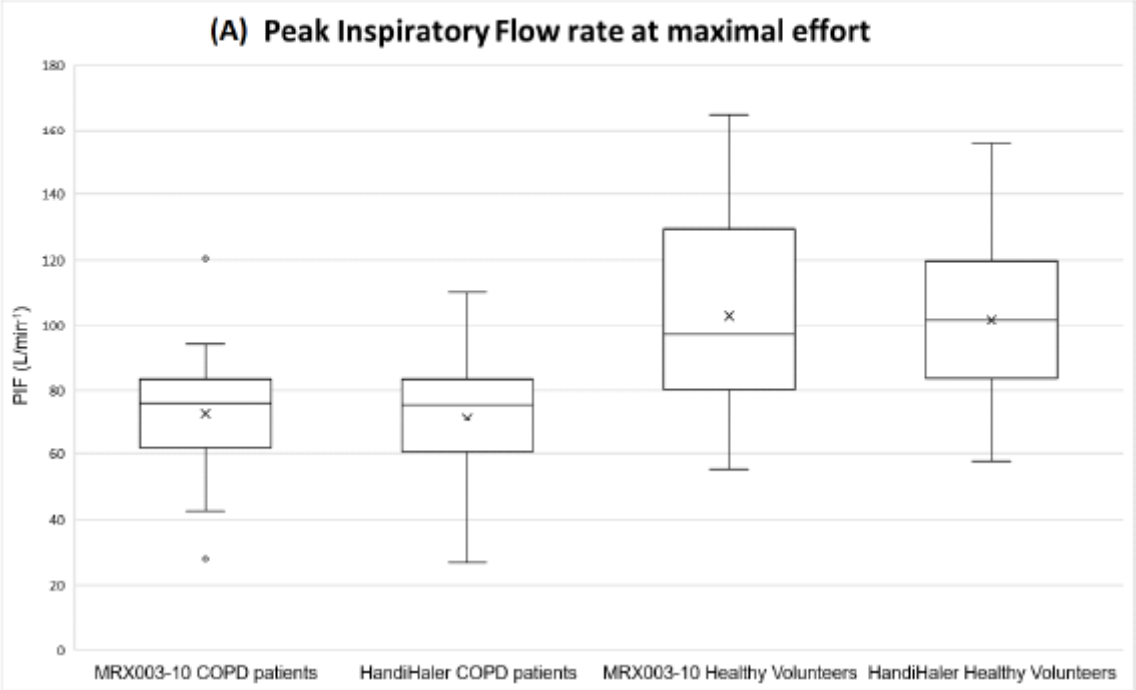
No studies were conducted as therapeutic equivalence is documented based on pharmacokinetics.

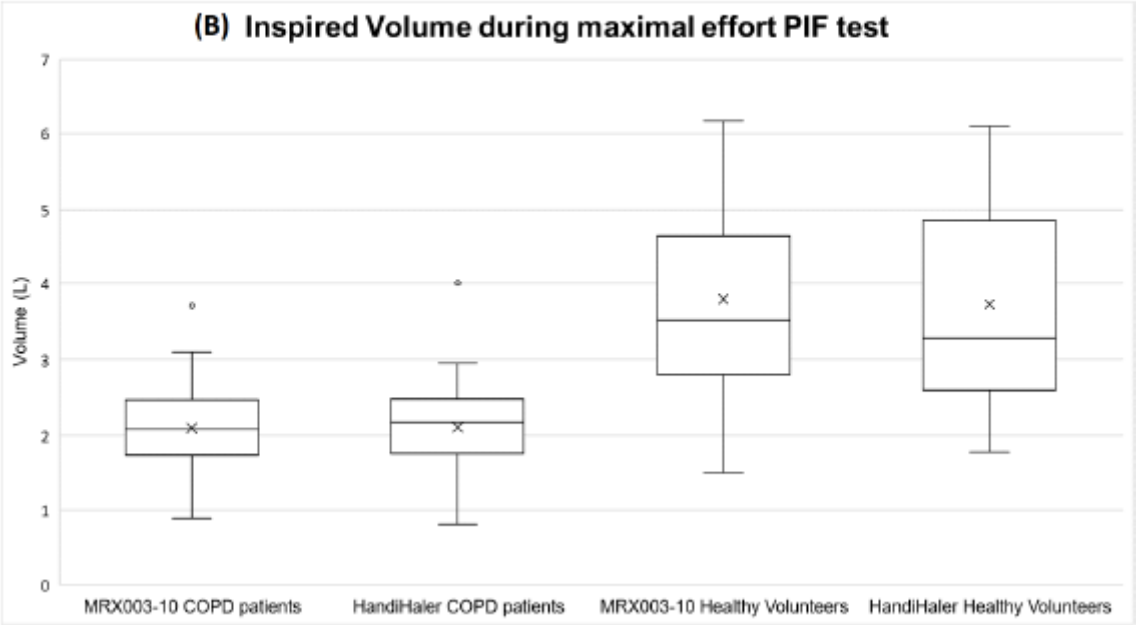
PIFR-study

Study MRX-H1118/73 was performed to collect data on peak inspiratory flow rates (PIFR) when inhaling from the MRX003-T10 device and the reference HandiHaler device. The study was an open label, single-centre, cross-over study and was performed in healthy volunteers and COPD patients. The study was intended to demonstrate that the COPD patients can inhale through the devices sufficiently to receive aerosolized medication and to understand the difference between the inspiratory flow rate performance characteristics of healthy volunteers and COPD patients. At a single visit, subjects were asked to inhale quickly and deeply from the inhalation devices until their lungs were full. Test and reference inhalers were connected in sequence with a spirometer to allow the measurement of PIFR and other inspiratory characteristics through each device. The process was repeated until three PIFR results were obtained for each inhaler. The highest PIFR obtained of at least three valid forced inspiratory attempts for each participant, per test device was used for the analysis.

Peak inspiratory flow rates and inspired volumes after inhalation through the MRX003-T10 and HandiHaler devices in healthy subjects and COPD patients are shown in the figure.

Figure 2.5. 5: Peak Inspiratory Flow rate (A) and inspired volume (B) in healthy subject and COPD patients via the MRX003-T10 device and Handihaler: MRX-H1118/73





The study showed no statistically significant differences (at the 0.05 level) between devices for the PIFRs attained in healthy volunteers or COPD patients. There were also no significant differences between devices for PIFRs achieved in moderate, severe and very severe COPD severity categories (defined per GOLD 2019). Additionally, no significant differences were identified between devices for inhaled volume, time to PIF, acceleration to PIF, inhalation times or FIVC/ IV ratio in either healthy volunteers or COPD patients.

Handling study

A handling study was performed, describe by the MAH in *P-016 Formative Study Report*, version 1.0, dated 15 Aug 2017

The results of the study are summarised as follows:
• No actual adverse events or suspected adverse events occurred or were otherwise reported during this study.

• In total, 20/22 (90%) participants were able to use the MRX003 device without committing more than 1 use error on any of the 13 primary objectives.

• In total, 19/22 (86%) of all participants were able to use the MRX003 device to inhale a simulated dose on first attempt.

• In total, 21/22 of users (96%) were able to use the MRX003 device to inhale a simulated dose on second attempt.

• Additionally, 19/22 of users (86%) performed 2 inhalations on their first attempt (1 was a study artefact due to the assumption of doing 1 inhalation for the study)

• During the subjective feedback portion, 2/11 (18%) of HandiHaler® users mentioned they typically only perform 1 inhalation with their HandiHaler®: Participant #010 does not typically perform two inhalations with HandiHaler®.

Participant #012 did not commit any use errors and performed 2 inhalations during the study. However, the participant mentioned they only typically perform one inhalation with their HandiHaler® but performed two because of the IFU instructed so.

• 4/22 (18%) of users pierced the capsule twice: Participant #006 inadvertently pressed again during inhalation
Participant #010 said they did not have confidence on first press
Participant #004 said they normally pierce twice with their Spiriva® capsules
Participant #019 assumed that the needle would go through the same hole and assumed it wouldn't matter if she pierced again for confidence

IV.4 Risk Management Plans

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 Tiogiva.

Updated Safety specification, RMP version 0.2, signed 14 April 2020

Summary of safety concerns	
Important identified risks	None
Important potential risks	Cardiac mortality
	Cardiac disorders (ischaemic heart disease including myocardial infarction and angina pectoris, cardiac arrhythmia, cardiac failure)
Missing information	Pregnant and breast-feeding women
	Patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure

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 V0.2 signed 14 April 2020 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 an RMP coincide, they can be submitted at the same time, but via different procedures.

IV.5 Discussion on the clinical aspects

No studies regarding clinical efficacy or safety were conducted as therapeutic equivalence is documented based on pharmacokinetics.

The results from the PIF study showed equivalence in required inspiratory flow between the test inhaler and its reference product.

The handling study showed that handling and inhalation procedure is very similar to that of the reference product, the Spiriva Handihaler.

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

The quality of the generic product, product name, is found adequate. There are no objections to approval of product name, 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 application is therefore recommended for approval.

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 Tiogiva, 18 µg, Inhalation powder, hard capsule. was positively finalised on 2020-10-08.

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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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