COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tiotropium Elpen 10 microgram inhalation powder, pre-dispensed (tiotropium bromide monohydrate)

NL/H/4920/001/DC

Date: 20 May 2022

This module reflects the scientific discussion for the approval of Tiotropium Elpen 10 microgram inhalation powder, pre-dispensed. The procedure was finalised on 8 September 2021. 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
PK	Pharmacokinetic
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 Member States have granted a marketing authorisation for Tiotropium Elpen 10 microgram inhalation powder, pre-dispensed, from Elpen Pharmaceutical Co. Inc.

The product is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Spiriva Handihaler 18 µg inhalation powder which has been registered in The Netherlands (RVG 26191) by Boehringer Ingelheim International GmbH since October 2001.

The concerned member states (CMS) involved in this procedure were Cyprus, Germany, Greece and Italy.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, i.e. a hybrid application. Since the pharmaceutical form of the proposed product (inhalation powder, pre-dispensed) is different to the reference product (inhalation powder, hard capsule), this type of application is appropriate.

II. QUALITY ASPECTS

II.1 Introduction

Tiotropium Elpen is a pre-dispensed white inhalation powder. Each unit dose blister strip contains 16 microgram tiotropium bromide monohydrate equivalent to 13 microgram tiotropium. The delivered dose is 10 microgram tiotropium.

One Elpenhaler device which contains 30 unit dose paper/PET/aluminium-PVC/aluminium/OPA blister strips, is packed in a PET/ALU/PE pouch together with a desiccant sachet. The PET/ALU/PE pouch is packed in a carton box together with the patient information leaflet.

The excipient is lactose monohydrate.

II.2 Drug Substance

The active substance is tiotropium bromide monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is white or yellowish-white powder or crystals and is sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride.

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 Ph.Eur.

Manufacturing process

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

Quality control of drug substance

The control tests and specification for drug substance are adequately drawn up. The quality of the active substance is controlled by the current version of the Ph. Eur. monograph of tiotropium bromide monohydrate. Tests for residual solvents and particle size are mentioned in CEP and these parameters are included in active substance specifications from the finished product manufacturer since micronised substance is used in the manufacture of the drug product. The MAH has justified the omission of a microbiological purity test. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 24 months when packed in double polyethylene bags in a triple laminated bag (polyethylene/terephthalate/aluminium/polyethylene), placed in an aluminium container. No special storage conditions are necessary. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The pharmaceutical development of the product has been adequately performed. The choice of excipient is justified and their functions explained. Lactose monohydrate of two different grades is used. The development is based on the reference product and has followed EMA´s guideline on inhalation products (EMA/CHMP/QWP/4913/2005).

Extensive formulation studies have been performed that cover active substance particle size and solid state evaluation, excipients levels optimisation and inhalation device selection. Polymorphism of the active substance has been discussed. The crystalline form is used and is considered to be stable and no conversion of polymorphic form is expected.

For development purposes four pharmacokinetic (PK) studies have been performed. One study only - a pivotal PK study, is relevant for the conclusion of the therapeutic equivalence. Other development studies performed were: physical characterisation, minimum fill, delivered dose and fine particle mass through container life and over patient flow range, single dose fine particle mass, actuator/mouthpiece deposition, cleaning requirements, effect on environmental moisture and robustness. These have followed the EMA guideline. It has been confirmed that the studies were conducted with the proposed device.

Results of bioequivalence studies have been submitted to support therapeutic equivalence in this hybrid application, which will be discussed in section IV on Clinical aspects.

Manufacturing process

The manufacturing process description is presented in sufficient details. The process consists of the preparation of a blend, mixing and filling into blisters. Taking into account the pharmaceutical form and the active substance content, the manufacturing process is considered to be a non-standard process. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipient complies with Ph.Eur. requirements. The specification of both grade lactose is set in line with the particle size results of the lactose monohydrate batches used for the PK study. These specifications are acceptable.

Microbiological attributes

The tests proposed for the microbial bioburden comply with the requirements of the Ph.Eur. for this type of product.

Bioburden of the built-in-the-mouthpiece powder

Furthermore, the possibility of any bioburden in the built-in powder during the patient use was investigated throughout the stability studies. The scope was to investigate the possibility of the presence of bioburden after patient use for the prescribed time period. This was carried out at specific time points at both long term conditions of storage of the product. It was adequately demonstrated that no mouthpiece bioburden exists after the expected in-use time period.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, uniformity of delivered dose, fine particle dose, total quantity deposited, water content, related

substances and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical except for any unspecified impurity and a specific impurity. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from four full scale batches and two pilot scale batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three full scale batches and two pilot scale batches stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. The photosensitivity was controlled according to the EMA guideline (ICH Q1B). A photostability study was performed and showed that the product is sensitive to light without its primary packaging. The primary packaging (blisters) protects the powder from the light.

On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture. After first opening of the aluminium pouch, use within 60 days, stored below 25°C. Write the date of first opening of the pouch on the sticker provided on the pouch. Place the sticker on the bottom of the device. Discard the aluminium pouch and the desiccant sachet."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM on lactose have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

Handling studies

The MAH has submitted more information on the medical device. The MAH briefly described changes implemented in the design of the device during the development and justified that no usability studies are necessary since evidence of usability for Elpenhaler device can be derived from data on previously approved drug-device combinations developed and marketed by Elpen Pharmaceutical. It is explained that currently all Elpenhaler devices share the same user interface, instructions for use and handling steps. References to publications were submitted where patient satisfaction and possible errors of Elpenhaler were evaluated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tiotropium Elpen 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

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tiotropium Elpen is intended for hybrid substitution of a similar product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Spiriva Handihaler 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tiotropium bromide monohydrate 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 hybrid application, the MAH has submitted a pivotal bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tiotropium Elpen 10 microgram inhalation powder, pre-dispensed (Elpen Pharmaceutical Co. Inc., Greece) is compared with the pharmacokinetic profile of the reference product Spiriva Handihaler (Boehringer Ingelheim International GmbH, Germany).

The choice of the reference product is justified by *in vitro* data. The data showed that both the test and reference product have a comparable linear flow rate dependency for fine particle dose and drug dosage. It is also sufficiently justified how the pharmacokinetic results

obtained in healthy volunteers can be extrapolated to the target population i.e. COPD patients. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, two-stage, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male and female subjects, aged 18-65 years. Each subject received one dose of the test tiotropium bromide monohydrate formulation (2x13 mcg/inhalation) or of the reference formulation (2x18 mcg/inhalation). The doses were received after at least ten hours of fasting. All inhalations of each treatment took place within one minute. There were two dosing periods, separated by a washout period of 14 days. Blood samples were collected pre-dose and at 0.0333, 0.0667, 0.1167, 0.1667, 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 9.0, 12.0, 16.0, 20.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. In this study, activated charcoal was not administered. In line with *Q&A document on Clinical Pharmacology and Pharmacokinetics*, in case the absorption of the drug in the lung is very quick (e.g., $t_{max} \leq 5$ minutes), like for tiotropium, and absorption occurs before the contribution of gastrointestinal absorption is significant, one study without active charcoal blockade is sufficient. In such case, $AUC_{0\text{-}30min}$ might be acceptable as a surrogate for efficacy, and $AUC_{0\text{-}t}$ for safety.

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 were withdrawn from the study due to positive results to drug of abuse tests (one subject), a positive result for pregnancy (one subject) and due to the intake of concomitant medication (one subject). 39 subjects were eligible for pharmacokinetic analysis. However, ten subjects had the C_{max} at the 1st sampling point. Pharmacokinetic parameters are shown in Table 1 and 2, including and excluding the ten subjects with C_{max} at the 1st sampling point, respectively.

Table 1. Pharmacokinetic parameters (arithmetic mean ± SD, t_{max} (median, range)) of tiotropium bromide monohydrate under fasted conditions.

Treatment N=39	$AUC_{0-0.5}$ (pg.h/ml)	AUC_{0-72} (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	5.22 ± 3.00	91.09 ± 29.8	18.61 ± 12.81	0.067 (0.033 – 0.167)
Reference	5.15 ± 2.96	89.28 ± 30.8	18.85 ± 12.74	0.067 (0.033 – 0.117)
***Ratio (94.12% CI)**	1.04 (0.92 – 1.08)	1.016 (0.93 – 1.09)	0.94 (0.82-1.08)	-

$AUC_{0-0.5}$	area under the plasma concentration-time curve from time zero to 30 minutes
AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
CI	confidence interval
t_{max}	time for maximum concentration

**ln-transformed values*

Table 2. Pharmacokinetic parameters (geometric means) of tiotropium bromide monohydrate under fasted conditions.

Treatment N=29	$AUC_{0-0.5}$ (pg.h/ml)	AUC_{0-72} (pg.h/ml)	C_{max} (ng/ml)
Test	5.07 ± 2.91	90.840	17.02 ± 11.72
Reference	4.86 ± 2.60	88.299	16.76 ± 10.48
***Ratio (94.12% CI)**	0.99 (0.89 – 1.10)	1.03 (0.94 – 1.13)	0.95 (0.85 – 1.07)

$AUC_{0-0.5}$	area under the plasma concentration-time curve from time zero to 30 minutes
AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
CI	confidence interval

**ln-transformed values*

Conclusion on bioequivalence study

The MAH has submitted pharmacokinetic and statistical analysis for $AUC_{0-0.5h}$ (as a surrogate for efficacy), AUC_{0-72h} (as a surrogate for the safety), C_{max} and t_{max}. The 94.12% CI for $AUC_{0-30min}$ were within the acceptance range of 0.80-1.25, both when ten subjects with C_{max} at the 1st sampling point were included and excluded. Thus, equivalence with regard to efficacy has been demonstrated.

Furthermore, the equivalence with regard to AUC_{0-72h} and C_{max} has been demonstrated. The MAH has submitted statistical analysis including and excluding the ten subjects with C_{max} at the 1st sampling point. Bioequivalence has been demonstrated for both C_{max} and AUC_{0-72} as 94.12% CI were within the limits of 0.80-1.25. Taken into account the totality of the data, i.e. including analysis with the subjects having C_{max} at the 1st sampling point, it can be concluded that equivalence regarding C_{max} and AUC_{0-72} has been established as well. In conclusion,

based on the submitted bioequivalence study, Tiotropium Elpen is considered bioequivalent to Spiriva Handihaler.

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).

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 Tiotropium Elpen.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• Cardiac mortality • Cardiac disorders (ischaemic heart disease including myocardial infarction and angina pectoris, cardiac arrhythmia, cardiac failure). • Medication errors
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

Next to routine pharmacovigilance activities and routine risk minimisation measures, the MAH committed to take additional risk minimisation measures (including educational material) pursuant to Article 21a or Article 22 of Directive 2001/83/EC.

- Prior to the launch of Tiotropium Elpen in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication and distribution modalities, and any other aspects of the programme, with the National Competent Authority.
- The MAH shall ensure that in each Member State where Tiotropium Elpen is marketed, all healthcare professionals involved in the field of respiratory medicine are provided educational material for HCPs.
- The educational material for HCPs shall comprise advice to minimise the potential risk of medication error and to indicate that although there are differences between Tiotropium Elpen and the originator product (Spiriva® HandiHaler® – tiotropium bromide) with respect to the pre-metered dose, both products provide the same delivered dose to the patient, and as such the strengths for both products are the same. The nominal dosing

schedule of one capsule/unit dose once daily is the same for Tiotropium Elpen and the originator product (Spiriva® HandiHaler® – tiotropium bromide).

IV.4 Discussion on the clinical aspects

For this hybrid authorisation, reference is made to the clinical studies and experience with the innovator product Spiriva Handihaler. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. The change in pharmaceutical form has been adequately discussed and is acceptable. A clinical overview with relevant references was provided and no new clinical studies were required. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) 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. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Tiotropium Elpen 10 microgram inhalation powder, pre-dispensed has a proven chemical-pharmaceutical quality and is a hybrid form of Spiriva Handihaler 18 microgram inhalation powder, pre-dispensed. Spiriva Handihaler is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tiotropium Elpen with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 8 September 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse