COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tiotropium ADOH 18 microgram, inhalation powder, hard capsule (tiotropium bromide monohydrate)

NL/H/5809/001/DC

Date: 7 May 2026

This module reflects the scientific discussion for the approval of Tiotropium ADOH 18 microgram, inhalation powder, hard capsule. The procedure was finalised on 14 October 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 ADOH 18 microgram, inhalation powder, hard capsule, from ADOH B.V.

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

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application. The efficacy and safety of "Tiotropium ADOH 18 microgram" is based on *in-vitro* studies and an overview of the literature.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Spiriva 18 microgram, inhalation powder, hard capsule, by Boehringer Ingelheim International GmbH (NL/H/0299/001) which has been registered in the Netherlands via national procedure (RVG 26191) since 9 October 2001.

The concerned member states (CMS) involved in this procedure were Germany and Poland.

II. QUALITY ASPECTS

II.1 Introduction

Tiotropium ADOH is a transparent hard capsules containing the inhalation powder. Each capsule contains as active substance 22.5 microgram tiotropium bromide monohydrate equivalent to 18 microgram tiotropium. The delivered dose (the dose that leaves the mouthpiece of the RS01 inhaler) is 10 microgram tiotropium.

The excipients are: lactose monohydrate (which may contain small amounts of milk proteins).
Hard capsule: hypromellose.

The hard capsules are packed in high density polyethylene (HDPE) bottle with polypropylene/high density polyethylene/low density polyethylene (PP/HDPE/LDPE) screw-cap closure; the cap contains silica gel as desiccant.
The RS01 inhaler is composed by Acrylonitrile-Butadiene-Styrene (ABS), stainless steel AISI 302 and Methyl Methacrylate-Acrylonitrile-Butadiene-Styrene (MABS).

The RS01 inhaler is a single dose inhalation device, made from plastic materials and stainless steel, with a body, coloured cap and coloured push buttons.

The RS01 inhaler is packed/available in each cardboard box.

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 a white or yellowish-white powder or crystals, and is sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride. The micronized drug substance is manufactured in the crystal form similar to the drug substance in the reference product. Stereochemistry is defined by the natural origin of the starting material and not further controlled.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP. The Ph.Eur. identity tests have been replaced by in-house RAMAN and the potentiometric assay has been replaced by in-house HPLC assay. An additional in-house Power Spectral Density (PSD) test has been added which differs from the test and limits provided in the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The choice of excipients is justified and their functions explained. The objective was to develop a medicinal product therapeutically equivalent to the currently marketed reference product Spiriva, inhalation powder, hard capsule, 18 microgram. Besides the regular formulation, manufacturing process development and scale up studies also all required specific pharmaceutical development studies for inhalation products have been adequately performed in line with EMA guideline on the pharmaceutical quality of inhalation and nasal

products. Multiple EU reference product batches have been characterised in support of the development studies and setting of the related drug product specifications. The effect of environmental moisture on the capsules stored outside the HDPE container has been adequately laid down and is comparable to the reference product.

Demonstration of therapeutical equivalence solely based on *in-vitro* data is acceptable for this application. Although the mouthpiece differs between the test (RS01) and reference product device the inhalation instruction is similar (the patient should inhale long, slow and deep). The device intrinsic resistance of the reference and test product devices are comparable over a flow rate of 10-90 L/min. Also the flow rate dependency is considered sufficient similar over a range of 20-70 L/min based on delivered dose (DUSA) and fine particle dose (NGI) data. Hence the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of tiotropium blending with sieved lactose including high shear mixing, filling of the blend and encapsulation in hydroxypropyl methylcellulose (HPMC) capsules. The manufacturing process has been validated according to relevant European/ICH 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 lactose monohydrate complies with Ph.Eur. requirements supplemented by a test on PSD. The functionality related characteristics and microbiological tests have been adequately discussed and justified. For the HPMC capsules a detailed in-house specification has been provided. The excipients specifications are acceptable.

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, water content, identification by HPLC retention time and UV, assay, average delivered dose, uniformity of delivered dose, fine particle dose, related substances (HPLC-MS and HPLC-UV) and microbial control. The release and shelf life limits differ with regard to the acceptance criteria for related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scaled validation batches stored at 25°C/60% RH (24 months), 30°C/ 75% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable ICH/European guidelines demonstrating the stability of the product for 24 months. Photostability studies were performed conform ICH Q1B demonstrating that the drug product is photo stable. On basis of the data submitted, a

shelf life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data have been provided demonstrating that the product remains stable for 30 days following first opening of the HDPE container, when stored at 25°C/60% RH, also at the end of the proposed shelf life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate, tiotropium bromide monohydrate and HPMC capsules 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tiotropium ADOH 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 ADOH is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Spiriva which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 is considered adequate. Although a limited number of clinical trials (approximately ten) were discussed, these were large phase 3 trials reflecting the main clinical benefits and risks of tiotropium bromide monohydrate 18 microgram inhalation powder. The member states agreed that no further clinical studies are required.

The SmPC is in accordance with the innovator's SmPC, except for the method of administration section 4.2 (differences in appearance and handling). The inhaler device is especially designed for Tiotropium ADOH and different from the innovator's HandiHaler used in combination with Spiriva inhalation powder. Both devices are breath actuated high resistant dry powder inhalers that employ pre-metered doses in the form of capsules. Although the opening of the device differs between the two devices, i.e. turning of the mouthpiece in the direction of the arrow (sidewards) for the test product inhaler versus pulling of the mouthpiece upwards for the Handihaler, further handling instructions are similar. The method to open the mouthpiece and pierce the capsule is also very similar to another marketed inhaler (i.e. Cyclohaler). The MAH adequately demonstrated that the handling of the RS01 Plastiape inhaler device is similar to the reference product device (HandiHaler).

Furthermore, the amount of the excipient lactose monohydrate is higher with Tiotropium ADOH (12.48 mg) compared to the innovator (5.5 mg). There are no safety concerns regarding this amount of lactose since there are several registered dry powder inhalers that have been marketed in the EU with lactose monohydrate quantities up to 25 mg.

IV.2 Pharmacokinetics

No new pharmacokinetic data has been provided. The MAH has claimed *in-vitro* equivalence between test and reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (version 0.2 signed 06 February 2024), 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 Triotropium ADOH.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Spiriva. No new clinical studies were conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

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: two rounds with 10 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 ADOH 18 microgram, inhalation powder, hard capsule has a proven chemical-pharmaceutical quality and is a hybrid form of Spiriva 18 microgram, inhalation powder, hard capsule. Spiriva is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence is demonstrated with the reference product in *in-vitro* studies.

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 ADOH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 October 2024.

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
NL/H/5809/001/IA/001	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a manufacturer responsible for importation and/or batch release • Not including batch control/testing	Yes	19-03-2025	Approved	N/A
NL/H/5809/IB/002/G	Change in the (invented) name of the medicinal product • for Nationally Authorised products Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use • Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	Yes No	06-02-2026	Partially approved	Change in (invented) name refused by CMS.
NL/H/5809/IA/003/G	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).	No	13-03-2026	Approved	N/A

	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph • Updated certificate from an already approved manufacturer	No			