COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Glycopyrronium DOC 44 microgram, inhalation powder in hard capsule (glycopyrronium bromide)

NL/H/5894/001/DC

Date: 31 July 2025

This module reflects the scientific discussion for the approval of Glycopyrronium DOC 44 microgram, inhalation powder in hard capsule. The procedure was finalised on 25 September 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
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
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
OIP	Orally Inhaled Products
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
µg	Microgram

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Glycopyrronium DOC 44 microgram, inhalation powder in hard capsule, from DOC Generici S.r.l.

The product is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult 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.

This decentralised procedure concerns a hybrid application using as reference the innovator product Seebri Breezhaler 44 mcg inhalation, which has been registered in the in the EEA via the centralised procedure EU/1/12/788 (NL license RVG 110668) by Novartis Europharm Limited since 28 September 2012.

Glycopyrronium DOC 44 microgram is claimed to be therapeutically equivalent to the reference medicinal product Seebri Breezhaler 44 mcg inhalation. Both medicinal products contain the active substance glycopyrronium bromide, in the same amount (44 µg) and concern the same pharmaceutical form which is a inhalation powder, hard capsule provided with an inhalation device. To justify therapeutical equivalence, the MAH refers to *in vitro* study data in line with the EMA guidelines for Orally Inhaled Products (OIP) CPMP/EWP/4151/00 Rev. 1. In addition, one pivotal pharmacokinetic study have been submitted to demonstrate equivalent lung deposition for the current product and the reference product.

The concerned member state (CMS) involved in this procedure was Italy.

II. QUALITY ASPECTS

II.1 Introduction

Glycopyrronium DOC 44 microgram is presented as a capsule in a blister and is administrated with the provided single-dose inhaler medical device (reused inhaler). The drug product is a white or almost white inhalation powder in a hard capsule with an orange transparent cap and a colourless transparent body. Each capsule contains as active substance 63 µg glycopyrronium bromide equivalent to 50 µg glycopyrronium. One capsule is equivalent to a single dose. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 55 µg glycopyrronium bromide equivalent to 44 µg glycopyrronium.

The excipients are:
Capsule content - lactose monohydrate (may contain milk protein) and magnesium stearate.
Capsule shell- hypromellose, potassium chloride, carrageenan, FD & C Yellow and purified water.

The capsules are packed in polyamide/aluminium/polyvinyl chloride/aluminium (PA/Alu/PVC-Alu) blisters. The inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl methacrylate acrylonitrile butadiene styrene. The needles and springs are made from stainless steel. As indicated in the SmPC, the blisters may be packed with or without the inhaler.

II.2 Drug Substance

The active substance is glycopyrronium bromide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white powder soluble in methanol, ethanol (96%) and hydrochloric acid; freely soluble in water (pH range of 1.2 to 7.5) and 1 M sodium hydroxide; very slightly soluble in acetic acid methylene chloride; practically insoluble in acetonitrile, chloroform and diethyl ether. It is chiral, containing two asymmetric carbons atoms and is a racemic mixture of the 3R/2S and 3S/2R stereoisomers. The active substance exists in one polymorphic form, the crystalline form A.

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. The proposed specifications are in line with the drug substance specification of the CEP holder with narrower limits for Particle Size Distribution (PSD). The specifications are acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The re-test period of the substance is 5 years 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 development of the product has been described, the choice of excipients is justified, and their functions explained. The choices of packaging and manufacturing process are adequately justified based on the dosage form. The composition and manufacturing process parameters have been investigated. Therapeutical equivalence was demonstrated based on pharmacokinetics (PK) studies. Development and equivalence studies have been performed in line with the EMA OIP guideline and the EMA guideline on the pharmaceutical quality of inhalation and nasal products. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is manufactured by blending the excipients and active substance in a low shear blender, followed by capsule filling which performs a full weight check. After filling, the capsules are packed in the primary packaging (blister), followed by the secondary packaging. The process is considered as a non-standard manufacturing process due to the specialised pharmaceutical dose form. Process validation data on the product have been submitted for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. These 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, identification, assay, related substances (individual and total impurities), water content (two methods), uniformity of dosage units, uniformity of delivered dose, mean delivered dose, aerodynamic particle size distribution (APSD), fine particle dose (FPD), impactor-sized mass (ISM) and microbial quality. The release and shelf-life limits are identical, with exception of the limits for related substances. Limits in the specification have been justified and are acceptable. An adequate risk evaluation report for nitrosamines has been provided. No risk for presence of nitrosamines in the drug product was identified. And adequate risk assessment for elemental impurities has been provided and it's in accordance with the ICH Q3D for products intended for inhalation administration, where Class 1, 1A and 3 elemental impurities are considered. The results showed that all levels of elemental impurities were below the 30% of Permitted Daily Exposure (PDE) established by ICH.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three 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 batches stored at 25°C/ 60% RH (18 months), 30°C / 65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European. Photostability studies in accordance with ICH recommendations showed that the proposed drug product is photostable. On basis of the data submitted, a shelf life was granted of 18 months (blister).

The labelled storage conditions are:

- Do not store above 25°C.
- The capsules must always be stored in the original blister in order to protect from moisture.
- The capsules must only be removed immediately before use.

Data have been submitted for the inhaler device demonstrating a lifetime of 90 uses, from the first use of the device. Based on this, the SmPC states:

- The inhaler from each pack or reused inhaler, should be disposed after 90 uses, counting from the first use of the inhaler.

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

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate 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 Glycopyrronium DOC 44 microgram 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 Glycopyrronium DOC 44 microgram is intended for hybrid 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 Seebri Breezhaler 44 mcg inhalation which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. As glycopyrronium is a widely used, well-known active substance, the MAH has not provided additional studies, instead 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

Glycopyrronium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. To support the application, the MAH submitted one pivotal PK study under fasting conditions and with healthy volunteers as described below.

IV.2 Pharmacokinetics

The MAH conducted one pivotal bioequivalence study in which the pharmacokinetic profile of the test product Glycopyrronium DOC 44 microgram, inhalation powder in hard capsule (DOC Generici S.r.l., Italy) was compared with the pharmacokinetic profile of the reference product Seebri Breezhaler 44 mcg inhalation (Novartis Europharm Limited, Ireland). The primary objective of this study was to evaluate the lung deposition comparing the two dry powder inhaler (DPI) formulations after a single dose in healthy subjects under fasting conditions. The secondary objective of this study was to evaluate the safety and tolerability of the drug treatments.

The MAH submitted a characterisation and complete set of comparative *in vitro* data for all three commercial reference batches as well as a rationale and comprehensive justification for the selection of the reference batch included in the pivotal PK study. It was sufficiently shown that the chosen reference batch was representative for commercial batches and had a good (the best) match with the test batch.

<u>Bioequivalence studies</u>

Study 1, fasted conditions (pivotal study)
Design
A single-dose, open label, randomised, four-period, two-treatment, two-sequence, crossover, replicate bioequivalence study was carried out under fasted conditions in 36 healthy male and 25 female subjects, aged 20-64 years. Subjects fasted at least 10 hours prior to drug administration and until at least 4 hours post-dose. Standardised meals were provided

throughout confinement and the meals were identical for all periods. Water consumption was restricted from one hour prior to drug administration until one our post-dose. Each subject received a single dose (44 µg, two oral inhalations from one hard capsule) of one of the two glycopyrronium formulations using their respectively Dry Powder Inhaler (DPI) devices. A standard protocol guided by the clinic staff was followed for drug administration, which consisted of a maximum of two attempts for the first inhalation and one attempt for the second inhalation. Clinic staff and subjects have previously undergone training with the DPI devices. Each subject was to use one device in each period. Used devices were not re-used. There were four dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose (within 90 minutes before dosing) and at 0.017, 0.033, 0.05, 0.067, 0.083, 0.10, 0.117, 0.133, 0.167, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 12, 16, 24, 48, and 72 hours after administration of the products.

The design of the study under fasted conditions is acceptable as Glycopyrronium may be taken without reference to food intake.

According to the EMA Q&A document (Clinical Pharmacology & Pharmacokinetics), the truncated $AUC_{0\text{-}30min}$ may be acceptable as a surrogate of efficacy in cases where the absorption of the drug in the lung is very quick (e.g., t_{max} ≤5 min) and where absorption occurs before the contribution of gastrointestinal absorption is significant. Both criteria apply to Glycopyrronium. Similarly, $AUC_{0\text{-}t}$ (systemic exposure) is acceptable as a surrogate of 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
For this study, 64 subjects were enrolled. Five subjects received at least one treatment A (test) and one treatment B (reference) and were included in the PK and statistical analysis. From these five, two subjects were discontinued due to a positive cotinine test, one after the second period and the other after the third period. One subject dropped out after the second period due to personal reasons. One subject was discontinued after the second period due a upper respiratory tract infection. One subject was discontinued after the third period due to an asymptomatic COVID-19 infection. Furthermore, three subjects did not accrue sufficient data for inclusion in the PK and statistical analyses. Two subjects dropped out after the first period due to personal reasons and one dropped out at the start of the second period due to incomplete dosing. A total of 61 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of glycopyrronium, 44 µg (two oral inhalations from one hard capsule) under fasted conditions.

Treatment N=61	AUC_{0-t} (pg/h/mL)	$AUC0_{-30min}$ (pg/mL/h)	AUC_{0-72} (pg/mL/h)	$AUC_{0-\infty}$ (pg/h/mL)	C_{max} (pg/mL)	t_{max} (h)
Test	318.49 (79.79)	43.59 (16.40)	321.94 (81.76)	474.55 (130.16)	192.75 (104.13)	0.05 (0.02-0.50)
Reference	338.30 (87.66)	51.77 (22.24)	341.47 (88.46)	489.29 (138.78)	240.63 (161.19)	0.05 (0.02-0.17)
***Ratio (90% CI)**	0.9471 (0.9199-0.9752)	0.8571 (0.8168-0.8993)	0.9401 (0.9137-0.9672)	0.9727 (0.9348-1.0121)	0.8460 (0.7899-0.9061)	---

$AUC_{0-\infty}$	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 the last measurable plasma concentration (t = 72 hours)
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:

Bioequivalence

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 study Glycopyrronium DOC 44 microgram is considered bioequivalent with Seebri Breezhaler 44 mcg inhalation.

Safety

The administration of the study drugs was generally well tolerated by the healthy subjects participating in this study. Overall, 17 Treatment Emergent Adverse Events (TEAEs) affecting 11 subjects (17.2% of subjects dosed) were reported during this study. Of these, 10 TEAEs affecting 6 subjects (9.4%) were assessed as being drug-related AEs (Adverse Events), probable or possible relationship to the treatment. Treatment A (test) was associated with 3 drug-related AEs affecting 2 subjects (3.2%), while treatment B (reference) had 7 drug-related AEs affecting 5 subjects (7.9%). Adverse events led to the discontinuation of 2 subjects (3.1%), however, the adverse events (upper respiratory tract infection and asymptomatic COVID-19, respectively) were assessed as unrelated to the drug treatments. No Serious Adverse Events (SAEs) were reported during the conduct of the study and none of the TEAEs compromised subject safety or had a significant impact on the integrity of the study results.

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 Pharmacodynamics

No pharmacodynamics studies have been conducted by the MAH to support this application for marketing authorisation. This is acceptable, as equivalent lung deposition has been shown. Therefore, no pharmacodynamic studies are mandatory in line with the OIP guideline (CPMP/EWP/4151/00).

Mechanism of Action

Preganglionic parasympathetic nerves innervate the airways via the vagus nerve. At parasympathetic ganglia, preganglionic nerves synapse with postganglionic nerves. Acetylcholine (ACh) is a neurotransmitter that is released during parasympathetic nerve impulses and acts by binding to and activating muscarinic receptors and nicotinic receptors. There are five muscarinic receptor subtypes, referred to as M1–M5. M1 receptors are highly expressed in the peripheral airways, whereas M2 and M3 receptors predominate in the larger airways. M3 receptors are the muscarinic receptors primarily responsible for ACh-induced bronchoconstriction, as they activate phospholipase C, which produces inositol 1,4,5-triphosphate and diacylglycerol, leading to intracellular calcium release. Anticholinergics block parasympathetic nerve impulses by selectively preventing ACh from binding to muscarinic receptors. These drugs inhibit bronchoconstriction in peripheral airways by antagonising the effects on airway smooth muscle cells of ACh released by epithelial cells, this release is stimulated by inflammatory cells.

IV.1 Clinical efficacy and clinical safety

No clinical development programme has been conducted by the MAH to support this application. An approach of the development program that comprises *in vitro* data only could be acceptable, provided that there are no differences in the active compound or in excipients, that lead to a difference in penetration of the active compound or local tolerance. (OIP guideline (CPMP/EWP/4151/00)). In this case equivalent lung deposition has been shown. Therefore, no clinical studies are mandatory in line with the OIP guideline (CPMP/EWP/4151/00). The test product showed the same flow rate dependency with the reference product. As such the results obtained with healthy volunteers can be extrapolated to the proposed target population.

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 Glycopyrronium DOC 44 microgram. At the time of approval, the most recent version of the RMP was version 1.0, DLP 28 June 2024, date of sign off 1 July 2024.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity including angioedema. • Atrial fibrillation.
Important potential risks	• Cerebrovascular events. • Cardiovascular event/Myocardial infarction. • Cardiovascular event/Heart failure. • Cardiovascular event/Cardiac arrhythmia. • Medication errors.
Missing information	• Use in unstable ischemic heart disease, arrhythmia and long QT-syndrome. • Use in pregnancy and lactation.

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

Periodic Safety Update Report (PSUR)
The active substance is currently not listed in the published EURD list. The MAH must submit the first periodic safety update report for this product with a period of 3 years (i. e. DLP of 36 months after authorisation) following authorisation. Also, the MAH must continuously check the European medicines web-portal to verify if the active substance has been included in the list of Union reference dates (EURD list). If so, after publication in the EURD list, the PSURs must be submitted in accordance with the requirements set out in the EURD list.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Seebri Breezhaler 44 mcg inhalation. The MAH demonstrated bioequivalence between Glycopyrronium DOC 44 microgram and the reference product. Also, for both products, the same flow rate dependency has been demonstrated. Therefore, the PK results obtained in healthy volunteers, which showed equivalent lung deposition comparing the test and reference product, can be extrapolated to the proposed target population. Risk management is adequately addressed. From a clinical point of view the application is approvable.

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.
A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Seebri Breezhaler 44 micrograms

inhalation powder, hard capsules (EU/1/12/788) for content and to Duloxetin Axiromed 90 mg and 120 mg magensaftresistente hartkapseln (from Laboratorios Liconsa). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Glycopyrronium DOC 44 microgram, inhalation powder in hard capsule has a proven chemical-pharmaceutical quality and is proven to be therapeutically equivalent to the reference product Seebri Breezhaler 44 mcg inhalation, which is a well-known medicinal product with an established favourable efficacy and safety profile.

For this application, therapeutically equivalence with the reference product has been demonstrated based on pharmaceutical data and pharmacokinetic studies. The chemical-pharmaceutical documentation in relation to Glycopyrronium DOC 44 microgram is of sufficient high quality in view of the present European regulatory requirements. Therapeutically equivalent 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 therapeutically equivalent has been demonstrated for Glycopyrronium DOC 44 microgram with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 September 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/5894 /001/IB/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation.	Yes	11-2-2025	Approved	N.A.