LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Indacaterol/Glycopyrronium Polpharma (indacaterol maleate, glycopyrronium bromide)

SE/H/2564/01/DC

This module reflects the scientific discussion for the approval of Indacaterol/Glycopyrronium Polpharma. The procedure was finalised on 2025-06-18. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Indacaterol/Glycopyrronium Polpharma, 85 mikrogram/43 mikrogram, inhalation powder, hard capsule.

The active substances are indacaterol maleate and glycopyrronium bromide. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Indacaterol/Glycopyrronium Polpharma, 85 mikrogram/43 mikrogram, inhalation powder, hard capsule, is a Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ultibro Breezhaler, 85 micrograms/43 micrograms, inhalation powder hard capsule, authorised in the Union since year 2013, with Novartis Europharm Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of indacaterol maleate and glycopyrronium bromide are well known. As indacaterol maleate and glycopyrronium bromide is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Indacaterol/Glycopyrronium Polpharma is a generic product, 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 Indacaterol/Glycopyrronium Polpharma from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
According to the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009), a step-wise approach should be considered when demonstrating therapeutic equivalence for an orally inhaled product. The first step consists of pharmaceutical data, the second step of pharmacokinetic data and the third step is represented by pharmacodynamic/clinical efficacy and safety data.

In the current application, equivalence was not demonstrated based on pharmaceutical data alone and thus pharmacokinetic studies were performed.

To support the marketing authorisation application the applicant has conducted 2 pivotal pharmacokinetic studies comparing Indacaterol/Glycopyrronium with the reference product Ultibro Breezhaler.

For indacaterol, the contribution of intestinal absorption to systemic exposure is not negligible and thus a study with (2023-5493) and without (2023-5422) activated charcoal was conducted. For glycopyrronium, the contribution of intestinal absorption to systemic exposure is not negligible but the absorption of the drug in the lung is very quick. Thus, a study without activated charcoal (2023-5422) was conducted.

Pharmacokinetic properties of the active substance
Indacaterol
Absorption: The median time to reach peak plasma concentrations of indacaterol was approximately 15 minutes.

Following inhalation, the absolute bioavailability of indacaterol has been estimated to range from 61 to 85% of the delivered dose.

Linearity: Systemic exposure to indacaterol increased with increasing (delivered) dose (120 micrograms to 480 micrograms) in a dose proportional manner.

Elimination: Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours.

Glycopyrronium
Absorption: The median time to reach peak plasma concentrations of glycopyrronium was approximately 5 minutes.

Following inahaltion, the absolute bioavailability of glycopyrronium was about 47% of the delivered dose.

Linearity: In COPD patients both systemic exposure and total urinary excretion of glycopyrronium at pharmacokinetic steady state increased about dose-proportionally over the (delivered) dose range of 44 to 176 micrograms.

Elimination: The mean terminal elimination half-life after inhalation was 33 to 57 hours.

Study 2023-5422, without charcoal

Methods

This was a single-dose, two-way, replicated crossover study conducted in healthy volunteers, comparing Indacaterol/Glycopyrronium, 85 µg/43 µg, hard capsules, with Ultibro Breezhaler, 85 µg/43 µg, hard capsules, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of indacaterol and glycopyrronium were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for C_{max}, $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}72h}$. The study was conducted between 2023-01-30 and 2023-02-28.

Results

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

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

Treatment	$AUC_{0\text{-}72h}$ pg*h/ml	$AUC_{0\text{-}30\ min}$ pg/ml	C_{max} pg/ml	t_{max} h
Test	**369.39 ± 107.93**	**47.21 ± 18.92**	**219.65 ± 111.21**	**0.05 (0.02-0.10)**
Reference	**341.92 ± 114.36**	**43.52 ± 21.51**	**198.75 ± 131.04**	**0.05 (0.02-0.13)**
***Ratio (90% CI)**	**110.85 (106.82-115.03)**	**114.21 (107.05-121.85)**	**120.72 (111.06-131.22)**	**-**

$AUC_{0\text{-}72h}$ area under the plasma concentration-time curve from time zero to 72 hours
$AUC_{0\text{-}30\ min}$ area under the plasma concentration-time curve from time zero to 30 minutes
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

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

Treatment	$AUC_{0\text{-}72h}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**1096.17 ± 352.27**	**219.49 ± 55.33**	**0.25 (0.17-0.35)**
Reference	**1214.62 ± 371.34**	**225.60 ± 67.60**	**0.25 (0.20-0.36)**
***Ratio (90% CI)**	**90.74 (87.77-93.82)**	**97.76 (94.58-101.05)**	**-**

$AUC_{0\text{-}72h}$ area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For glycopyrronium, for AUC_{0-72h} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %. For C_{max} the 90 % confidence interval for the ratio of the test and reference products did not fall within the conventional acceptance range of 80.00-125.00 %. A widened acceptance range of 75.83-131.87 was applied for C_{max}.

Study 2023-5493, with charcoal

Methods

This was a single-dose, two-way, replicated crossover study conducted in healthy volunteers, comparing Indacaterol/Glycopyrronium, 85 µg/43 µg, hard capsules, with Ultibro Breezhaler, 85 µg/43 µg, hard capsules, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of indacaterol were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for C_{max} and AUC_{0-72h}. The study was conducted between 2023-08-18 and 2023-10-09.

Results

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

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for indacaterol

Treatment	AUC_{0-72h} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**1010.94 ± 310.40**	**254.08 ± 61.98**	**0.25 (0.17-0.33)**
Reference	**925.07 ± 335.25**	**214.75 ± 61.13**	**0.25 (0.20-0.50)**
***Ratio (90% CI)**	**116.14 (110.58-121.97)**	**124.70 (118.79-130.91)**	**-**
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72h} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %. For C_{max} the 90 % confidence interval for the ratio of the test and reference products did not fall within the conventional acceptance range of 80.00-125.00 %.

Discussion and overall conclusion

For indacaterol, the contribution of intestinal absorption to systemic exposure is not negligible and thus a study with and without activated charcoal is adequate in order to assess equivalence regarding both efficacy and safety. For glycopyrronium, the contribution of intestinal absorption to systemic exposure is not negligible but the absorption of the drug in the lung is very quick (median t_{max} was 3 minutes in the study). Thus, for glycopyrronium, the use of $AUC_{0-30\ min}$ as a surrogate for efficacy in a study without activated charcoal can be accepted.

The overall study design in study 2023-5422 and 2023-5493 is satisfactory. Both studies were performed in healthy volunteers. Extrapolation of results from the PK study performed with healthy volunteers to the patient population is acceptable since the test and reference products have no flow rate dependency. The bioanalytical methods were adequately validated.

In study 2023-5422, similar systemic safety could be concluded for indacaterol. For glycopyrronium, a widened acceptance range was applied for C_{max}. This is deemed acceptable considering

glycopyrronium's relatively wide therapeutic window. The most important role for C_{max} in case of products acting locally in the lung is as an indirect marker for lung distribution, as a high C_{max} recorded at an early timepoint could signal absorption from a more central compartment in the lung, thus questioning whether exposure more distally in the lung is similar. In this case, t_{max} and the shape of plasma concentration-time curve during the absorption phase is similar, and the point estimates for both $AUC_{0\text{-}30min}$ and C_{max} are clearly above 1, which supports similar deposition pattern within the lung.

In study 2023-5493, similar pulmonary disposition could not be concluded for indacaterol. However, the applicant submitted data showing that C_{max} for the reference product in study 2023-5493 is not affected by gastrointestinal absorption. This argument was supported by literature data and by comparing the results of the study with and without charcoal performed by the applicant. Thus, C_{max} in both study with and without charcoal might be used as a surrogate for efficacy, where the study without charcoal has results within acceptance criteria and the study with charcoal has results above acceptance criteria. The point estimates for C_{max} differs between these studies; however this seems to be caused by C_{max} being clearly higher for the test product in the study with charcoal than in the study without charcoal. The reason for this finding is not understood, since charcoal administration would not be expected to increase C_{max}. Based on that the reference batches used in both study with and without charcoal are representative and similar to each other, the shape of the plasma concentration time profile is similar between the test and reference product (thus not indicating different deposition pattern in the lung) and that therefore marginally higher C_{max} (if true) would not be expected to translate to impaired efficacy, therapeutical equivalence can be concluded for indacaterol.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Indacaterol/Glycopyrronium Polpharma.

Part II Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is considered acceptable.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 04-Dec-2024 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 a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Ultibro Breezhaler, (EMEA/H/C/002679/0000) regarding content and Rimal (national procedure MA no 23832-23835) regarding design/layout.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Indacaterol/Glycopyrronium Polpharma, is found adequate. There are no objections to approval of Indacaterol/Glycopyrronium Polpharma, 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 benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Indacaterol/Glycopyrronium Polpharma, 85 mikrogram/43 mikrogram, Inhalation powder, hard capsule was positively finalised on 2025-06-18.

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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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se