LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Indacaterol/Glycopyrronium Viatris
(glycopyrronium bromide, indacaterol maleate)

SE/H/2817/001/DC

This module reflects the scientific discussion for the approval of Indacaterol/Glycopyrronium Viatris. The procedure was finalised at 2026-07-01. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Indacaterol/Glycopyrronium Viatris, 85 mikrogram/43 mikrogram, Inhalation powder, hard capsule.

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

II. EXECUTIVE SUMMARY

II.1 About the product

The Indacaterol/Glycopyrronium Viatris contains indacaterol and glycopyrronium and is intended for a once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Indacaterol is a long-acting beta2-adrenergic agonist (LABA). When inhaled, indacaterol acts locally in the lung as a bronchodilator.

Glycopyrronium is a long-acting muscarinic receptor antagonist (LAMA). Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

II.2 General comments on the submitted dossier

The application for Indacaterol/Glycopyrronium Viatris, 85/43 micrograms, 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 FR 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+43µg, inhalation powder, hard capsule, authorised in the Union since 2013, with Novartis Europharm Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted studies has been provided. No issues regarding GCP have been identified. The clinical and the bioanalytical facilities were inspected by the UK authority in 2018, without any critical findings and has also been inspected more recently by the FDA (2022/2023). No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
The product is a combination of indacaterol and glycopyrronium for the maintenance treatment of COPD. Ultibro Breezhaler (Novartis Europharm Limited) is stated as a reference product. Since the present product is designated for administration via inhalation, it is applied for MAA according to the article 10(3) (Hybrid Art.) of the Directive 2001/83/EC.
The present product has the same strength, indication, and posology as the reference product. The excipients in the capsule content are also the same between the two products, and the excipients of the capsule shell are widely known and commonly used in the pharmaceutical industry. The capsule contents are prepared for inhalation using an inhaler device. No differences have been identified

between the products, that would be expected to significantly affect their pharmacological or toxicological properties.
Pharmacodynamic, pharmacokinetic and toxicological properties of both active substances are well known. As active substances are widely used, no further non-clinical studies are required, nor does the Applicant provide any. Overview based on literature review is, thus, appropriate.
The non-clinical overview was written by Dr Joanna Pawlak and contains 49 references.

Environmental Risk Assessment (ERA)
The Applicant has submitted an ERA for indacaterol and glycopyrronium in their product. PECsw was calculated using default Fpen and the obtained PECsw values were 0.000425 ug/L and 0.000215 ug/L for indacaterol and glycopyronium, respectively. As both values are below 0.01 ug/L no further risk assessment is deemed necessary.
Based on the ERA for the reference product Ultibro Breezehaler (2013), indacaterol and glycopyrronium have logKow lower than 4.5 and therefore, no further PBT/vPvB assessment is required. The same conclusion is considered valid for the present product, according to the current ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*, 22 August 2024).

Conclusions:
Active substances' PEC surface water values are below the action limit of 0.01 µg/L and are not PBT substances as log Kow does not exceed 4.5.
Considering the above data, indacaterol and glycopyrronium are not expected to pose a risk to the environment.
There are no objections to approval of the present product from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
According to the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1 and Rev.2), a step-wise approach should be considered when demonstrating therapeutic equivalence for an orally inhaled product. 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 (one with and one without activated charcoal) comparing Indacaterol/Glycopyrronium, 85 µg/43 µg, hard capsules with the reference product Ultibro Breezhaler, 85 µg/43 µg, hard capsules. In addition, 4 pilot studies were performed.

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. Glycopyrronium concentrations were only measured in the pivotal study performed without activated charcoal blockade. 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 and it was proposed to use $AUC_{0\text{-}30\ min}$ as a surrogate for efficacy in the study without charcoal.

Pharmacokinetic properties of the active substances
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 48 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** **(N=163)**	**$AUC_{0\text{-}30\ min}$** **pg/ml** **(N=167)**	**C_{max}** **pg/ml** **(N=167)**	**t_{max}** **h** **(N=167)**
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_{0-72h} pg*h/ml (N=163)	C_{max} pg/ml (N=167)	t_{max} h (N=167)
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_{0-72h} 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 30 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, n=109.

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 %.

Post-hoc calculations

The applicant has performed additional analysis of the data obtained in the 2023-5493, which included the participants, who were firstly rejected from the per-protocol analysis because the remainings of the drug product were found in their inhalers after product administration. The applicant states that such protocol constraint is rational in the setting of a clinical trial; nevertheless, it does not correspond to the real world setting, when the test and reference products would be used by COPD patients. The higher variability in the inhalation effectiveness would be more than expected in such settings, according to the applicant.

Table 4. Summary of study results based on plasma indacaterol levels, including subjects that had drug product remaining in their inhalers after product administration

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_{72}	**A1**	29	889.07 (33)	934.13	**A vs B**	108.11	101.12 - 115.58	22
*(hr*pg/mL)*	**A2**	29	1085.42 (29)	.				
	B1	29	851.69 (35)	864.04				
	B2	28	1001.08 (36)	.				
C_{max}	**A1**	29	238.24 (26)	240.92	**A vs B**	116.99	109.94 - 124.49	20
(pg/mL)	**A2**	29	259.72 (25)	.				
	B1	29	214.91 (28)	205.93				
	B2	28	214.57 (29)	.				
Treatment A (Test)	*L9 Glycopyrronium/Indacaterol 43/85 µg inhalation powder, hard capsule using Inhaler Mora Ellipse DPI LR Nesat, Batch No.: B021022M (Zaklady Farmaceutyczne Polpharma S.A., Oddzial Medana w Sieradzu, Poland)*							
Treatment B (Reference)	*Ultibro® Breezhaler® 43/85 µg inhalation powder, hard capsules, Batch No.: BCVH3 (Novartis Europharm Limited, Ireland)*							

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 $AUC_{0\text{-}30\ min}$ 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 however 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 $AUC_{0-30min}$ and C_{max} are clearly above 1, which supports similar deposition pattern within the lung. The widened acceptance range is acceptable also from statistical perspective and thus similar efficacy and safety can be concluded for glycopyrronium.

In study 2023-5493, for indacaterol 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 %. The applicant performed post-hoc analysis, including the participants that were firstly rejected from the per-protocol analysis because remainings of the drug product were found in their inhalers, stating that this is real-world data. It should be noted that this post-hoc analysis was performed when the result of the primary analysis (not showing similarity) was available. It is not acceptable to include subjects that did not receive the intended dosing. Thus, for indacaterol, C_{max} in study 2023-5493 (with charcoal) was not within acceptance criteria for demonstration of equivalence regarding pulmonary deposition.

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 the 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}.

The updated version of the OIP guideline which has recently come into force generally states that therapeutic similarity with regard to efficacy can be concluded if the 90% CI for the ratio of the test and reference products is contained within the acceptance interval of 80.00-125.00 and that any deviations from these acceptance criteria must be thoroughly justified and can never be accepted for results below the lower limit of the acceptance range or when data on safety is generated from a study using different test and/or reference batches. The reason why results above the upper limit can never be accepted for studies using different test and/or reference batches is to prevent the MAHs purposely selecting batches for each study in order to show therapeutic equivalence regarding efficacy and safety respectively. Even though different references batches were used in the study with and without charcoal (although both are representative), the current application deviates from the conditions stated in the OIP guideline since C_{max} in the study with and without charcoal can both be used as surrogate for efficacy and has equal probability of being true. Thus, it may be possible to justify if the upper limit of the 90% CI is above 125.00 in one of the comparisons in the current case. 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 therefore marginally higher C_{max} (if true) would not be expected to translate to impaired efficacy. Overall, it can thus be concluded that the test product is therapeutically similar to the reference product regarding intacaterol, although Cmax for the test product is slightly higher in the study with charcoal.

In conclusion, therapeutic equivalence between test and reference product has been demonstrated based on pharmacokinetic data.

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.

Pharmacovigilance system
Proposed MAH: Viatris Limited, Viatris Santé

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Viatris.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

The reference medicinal product used for this procedure is Ultibro Breezhaler (43 micrograms of Glycopyrronium bromide and 85 micrograms of Indacaterol), inhalation powder, hard capsules. In the summary of safety concerns of Ultibro Breezhaler several safety concerns are listed. However, there are no additional pharmacovigilance activities or additional risk minimisation measures in place for any of the important identified, important potential risks and missing information listed in the safety specification of the reference products RMP. In addition, there are no clinical measures to address a certain risk beyond standard clinical practice. Therefore, in line with the definitions of important identified and important potential risks and missing information in GVP module V, revision 2, the proposed Summary of safety concerns with no included safety concerns as proposed by the applicant is supported.

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 endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 21 April 2026 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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Indacaterol/Glycopyrronium Viatris, is found adequate. There are no objections to approval of Indacaterol/Glycopyrronium Viatris, from a non-clinical and clinical point of view. Therapeutic equivalence between test and reference product has been demonstrated based on pharmacokinetic data.
The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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, EU/1/13/862/001-008 regarding content and to Rimal, CZ/H/513/1-4/DC regarding layout.

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

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-