LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Foracort
(budesonide, formoterol fumarate dihydrate)

SE/H/2511/01/DC

This module reflects the scientific discussion for the approval of Foracort. The procedure was finalised at 2025-05-07. For information on changes after this date please refer to the module 'Update'.

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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 Foracort, 160 micrograms/4,5 micrograms/actuation, pressurised inhalation, suspension.

The active substances are budesonide and formoterol fumarate dihydrate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

The application for Foracort, 160 µg/4.5 µg/actuation, pressurised inhalation, suspension, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The product contains the glucocorticoid budesonide and the β_2-stimulator formoterol which are combined in numerous products to be used in treatment of COPD.

II.2 General comments on the submitted dossier

The application for Foracort, 160 µg/4.5 µg/actuation, pressurised inhalation, suspension, 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 the following concerned member states (CMS):

SE/H/2511/01/DC: LU

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Symbicort Turbuhaler (SE/H//229/01), 160 microgram/4,5 microgram/inhalation, inhalation powder, authorised in Sweden since 2000, with AstraZeneca as marketing authorisation holder.

The reference product used in the pharmacokinetic studies is Symbicort, 160 microgram/4.5 microgram/actuation, pressurised inhalation, suspension (SE/H/229/03) from ES with Laboratorio AstraZeneca Farmacéutica Spain as marketing authorisation holder.

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.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that

acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substances acceptable statements/declarations are provided from the manufacturers responsible for batch release situated in the EU. It is confirmed that the drug substance manufacturer Cipla Limited Kurkumbh performs all manufacturing steps, including micronization and that the micronization step was included in the QP audit.

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 2019, without any critical findings. No inspection of the submitted pharmacokinetic 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
Pharmacodynamic, pharmacokinetic and toxicological properties of budesonide, formoterol fumarate dihydrate are well known. As budesonide, formoterol fumarate dihydrate are widely used, well-known active substances, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Since Foracort, 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 Foracort, 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, 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.

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted 3 pharmacokinetic studies comparing Budesonide and Formoterol Fumarate Dihydrate 160 microgram/ 4.5 microgram per actuation, pressurised inhalation, suspension with the reference product Symbicort, 160 micrograms/4.5 micrograms/actuation, Pressurised inhalation, suspension:

- Study 22-06-106, without administration of activated charcoal
- Study 22-06-105, with administration of activated charcoal (claimed to be intended as an exploratory study to investigate variability)
- Study 0058-12-22, with administration of activated charcoal

The pharmacokinetic studies were performed without spacer.

Pharmacokinetic studies aim at demonstrating similar pulmonary deposition and similar total systemic exposure between a hybrid inhalation product and the originator. According to the OIP guideline, bioequivalence studies with charcoal blockade could be used to compare pulmonary deposition as a surrogate for efficacy. In addition, bioequivalence studies without charcoal blockade could be used to compare systemic exposure as a surrogate for safety.

Pharmacokinetic properties of the active substance
Budesonide
Following inhalation of Symbicort (pressurised inhalation, suspension) maximal plasma concentrations of budesonide occur at approximately 30 minutes. Systemic exposure correlates in a linear fashion to administered dose. The terminal half-life (after IV dosing) is 4 hours.

Formoterol
Following inhalation of Symbicort (pressurised inhalation, suspension) maximal plasma concentrations of formoterol occur at approximately 15 minutes. Systemic exposure correlates in a linear fashion to administered dose. The terminal half-life is approximately 17 hours.

Study 22-06-106, without administration of activated charcoal
Methods
This was a single-dose, replicate design crossover study conducted in 66 healthy volunteers, comparing Budesonide and Formoterol Fumarate Dihydrate 160 microgram/ 4.5 microgram per actuation, pressurised inhalation, suspension with Symbicort, 160 micrograms/4.5 micrograms/actuation, Pressurised inhalation, suspension from the ES market at a dose of 2 puffs (total dose of 320 microgram/9 microgram of budesonide/formoterol) under fasting conditions and

without concomitant administration of activated charcoal. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of formoterol and budesonide were determined with two LC/MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 14th December 2022 and 13th January 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 and 2 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for budesonide, n=64 (128 observations for test and for reference).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**2666.60 ± 1107.13**	**809.74 ± 328.19**	**0.33 (0.08-1.02)**
Reference	**2739.87 ± 1086.42**	**808.04 ± 331.53**	**0.33 (0.08-2.02)**
***Ratio (90% CI)**	**95.75 (92.43-99.20)**	**99.45 (95.19-103.89)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **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 formoterol, n=64 (127 observations for test and for reference).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**50.35 ± 19.81**	**10.73 ± 5.20**	**0.11 (0.05-2.02)**
Reference	**55.77 ± 22.24**	**12.44 ± 6.33**	**0.11 (0.05-4.00)**
***Ratio (90% CI)**	**89.92 (86.41 - 93.57)**	**87.46 (82.97 - 92.20)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} 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 both budesonide and formoterol in this study without activated charcoal blockade.

<u>Study 0058-12-22, with administration of activated charcoal</u>
Methods
This was a single-dose, replicate design crossover study conducted in 66 healthy volunteers, comparing Budesonide and Formoterol Fumarate Dihydrate 160 microgram/ 4.5 microgram per actuation, pressurised inhalation, suspension with Symbicort, 160 micrograms/4.5

micrograms/actuation, Pressurised inhalation, suspension from the ES market at a dose of 2 puffs (total dose of 320 microgram/9 microgram of budesonide/formoterol) under fasting conditions and with concomitant administration of activated charcoal. A total of 50 mL of charcoal suspension (containing approximately 5 gm of activated charcoal in 50 mL water) was administered to the subjects immediately prior to the dosing, immediately after dosing and at 0.75 and 1.50 hours post-dose. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of formoterol and budesonide were determined with two LC/MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 8th June and 5th July 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 3 and 4 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for budesonide, n=66 (129 observations for test and 131 for reference).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**1812.31 ± 835.55**	**746.70 ± 373.59**	**0.25 (0.08-1.00)**
Reference	**1782.22 ± 808.49**	**719.43 ± 355.84**	**0.27 (0.08-0.77)**
***Ratio (90% CI)**	**100.73 (97.01-104.59)**	**102.75 (97.88-107.86)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for formoterol, n=66 (127 observations for test and 130 for reference).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**29.46 ± 15.87**	**10.18 ± 5.52**	**0.11 (0.05-0.33)**
Reference	**27.91 ± 15.42**	**9.46 ± 5.54**	**0.11 (0.05-0.50)**
***Ratio (90% CI)**	**103.67 (96.22-111.69)**	**109.14 (103.92-114.63)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} 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 both budesonide and formoterol in this study with activated charcoal blockade. T_{max} was also similar between test and reference.

Study 22-06-105, with administration of activated charcoal

Methods
This was a single-dose crossover study conducted in 36 healthy volunteers, comparing Budesonide and Formoterol Fumarate Dihydrate 160 microgram/ 4.5 microgram per actuation, pressurised inhalation, suspension with Symbicort, 160 micrograms/4.5 micrograms/actuation, Pressurised inhalation, suspension from the ES market at a dose of 2 puffs (total dose of 320 microgram/9 microgram of budesonide/formoterol) under fasting conditions and with concomitant administration of activated charcoal. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of formoterol and budesonide were determined with two LC/MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 4th January and 15th January 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 5 and 6 below.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for budesonide, n=35

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**1782.45 ± 809.21**	**690.52 ± 329.47**	**0.33 (0.08-0.75)**
Reference	**1697.16 ± 670.32**	**653.53 ± 298.74**	**0.33 (0.11-0.77)**
***Ratio (90% CI)**	**101.64 (91.93 - 112.36)**	**100.02 (89.46 - 111.82)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for formoterol, n=35

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**23.31 ± 12.12**	**7.91 ± 3.70**	**0.11 (0.08-0.42)**
Reference	**27.24 ± 13.81**	**9.82 ± 5.19**	**0.11 (0.05-0.42)**
***Ratio (90% CI)**	**82.48 (*74.44* - 91.38)**	**81.19 (*71.96* - 91.60)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} 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 budesonide in this study with activated charcoal blockade.

However, for formoterol the 90% CI for the ratio of the test and reference products for AUC_{0-t} and C_{max} did **not** fall within the conventional acceptance range of 80.00-125.00%. For both AUC_{0-t} and

C_{max} the lower limit of the 90% CI was below 80 and the point estimate was only slightly above 80.

No additional strengths are applied for.

Discussion and overall conclusion

The pharmacokinetic studies and their statistical evaluation were generally in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and in line with the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009) and related Q&As. The bioanalytical methods were adequately validated. The batches used in the studies are considered representative.

Exclusion of data for subjects where three to four consecutively measured formoterol concentration data points towards elimination phase were not available is not in line with the BE guideline, but in this case it was not considered likely that this exclusion would significantly affect the outcome of the studies. This was confirmed in an additional statistical analysis performed by the Applicant.

The pharmacokinetic studies were performed with and without activated charcoal blockade in order to compare both pulmonary deposition and total systemic exposure of budesonide and formoterol. This is adequate. Subjects were trained on inhalation technique and adequacy of inhalation was checked, which is important.

Extrapolation of results from the PK study performed with healthy volunteers to the patient population is acceptable since the test and reference products are pMDIs and thus have no flow rate dependency.

In studies 0058-12-22 and 22-06-105 there was a rather large number of observations where the extrapolated AUC was above 20% for formoterol. According to the BE guideline, if this occurs in more than 20% of the observations the validity of the study may need to be discussed. However, in this case sampling occurred for 72 hours and concentrations at the last time point were below LLOQ in most cases. Thus, a longer sampling than 72 hours is not considered necessary and no concern is raised.

In studies 0058-12-22 (with charcoal) and 22-06-106 (without charcoal), results were within BE criteria for both active substances. However, in study 22-06-105, results for budesonide were within acceptance criteria but results for formoterol were outside conventional acceptance criteria, indicating lower lung deposition for test product compared to reference product. The applicant also presented data on partial AUC from the study without charcoal. It may be possible to use an early partial AUC from a study without charcoal as efficacy parameter if lung absorption is sufficiently rapid (tmax at or below 5 minutes). This may be applicable for formoterol which has a rather quick lung absorption (although tmax was slightly above 5 minutes; 6.6 minutes, in study 22-06-106). Results for AUC0-30 min for formoterol were just within acceptance criteria, which provides some confirmation regarding equivalence in efficacy.

Thus, for formoterol, therapeutic equivalence has been demonstrated regarding safety. Regarding efficacy, there are two studies with activated charcoal: Study 22-06-105 which demonstrates lower lung deposition (smaller study, claimed to be intended as an exploratory study to investigate variability) and study 0058-12-22 which demonstrates equivalence in lung deposition (larger study, using a different test batch with a tendency to higher FPD). In addition, there is a study without charcoal that may also provide supportive data on efficacy by using partial AUC data since formoterol is rather rapidly absorbed from the lung: study 22-06-106 (same test batch as study 22-06-105, also with a tendency to lower systemic exposure and lung deposition (as measured by $AUC_{0\text{-}30\ min}$ and C_{max}), but with results within acceptance criteria). Although all batches used are considered representative, there is a tendency to lower FPD for the test batch used in studies 22-06-105 and 22-

06-106 (the same reference batch was used in all studies), which is consistent with a lower exposure of test product compared to reference product seen in these studies. Taken together, the submitted documentation is considered sufficient to conclude on therapeutic equivalence regarding formoterol.

For budesonide, therapeutic equivalence regarding efficacy was demonstrated in both studies with activated charcoal (study 22-06-105 and study 0058-12-22) and therapeutic equivalence regarding safety was demonstrated in study 22-06-106.

All pharmacokinetic studies have been performed without spacer. As discussed in the Quality part, in vitro equivalence with spacer has been demonstrated. Thus, there is no need to perform PK studies with spacer.

In conclusion, based on the submitted pharmacokinetic studies, therapeutic equivalence without spacer has been demonstrated for Budesonide and Formoterol Fumarate Dihydrate 160 microgram/ 4.5 microgram per actuation, pressurised inhalation, suspension compared to Symbicort, 160 micrograms/4.5 micrograms/actuation, Pressurised inhalation, suspension. In vitro data with spacer fulfils acceptance criteria for demonstration of TE, thus pharmacokinetic studies with spacer are not needed.

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 in RMS/CMS: Cipla Europe NV, Belgium

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 Foracort.

Part II Safety specification

Table SVIII.1: Summary of safety concerns[4]

Summary of safety concerns	
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 endorsed.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.1 signed 27.10.2023 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 hybrid product, Foracort, is found adequate. There are no objections to approval of Foracort, from a non-clinical and clinical point of view. Therapeutic equivalence between the test and reference product has been adequately demonstrated using pharmacokinetic data (comparison without spacer) and in vitro data (comparison with spacer). 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

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to 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

The package leaflet 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. Assessment of the User Testing is attached in Appendix I.

The results show that the package leaflet 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.

V.5 Labelling

The approved Labelling is available in the MRI Product Index.

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
-	-	-	-	-	-