COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Beclometasondipropionaat/formoterolfumaraat-dihydraat 100/6 microgram/dose and 200/6 microgram/dose Vincion, aërosol, solution (beclometasone dipropionate/ formoterol fumarate dihydrate)

NL License RVG: 129826 and 129831

Date: 29 June 2026

This module reflects the scientific discussion for the approval of Beclometasondipropionaat/formoterolfumaraatdihydraat 100/6 microgram/dose and 200/6 microgram/dose Vincion, aërosol, solution. The procedure was finalised on 10 November 2023. 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
CPMP	Committee for Proprietary Medicinal Products
ECG	Electrocardiogram
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
MO	Major Objection
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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the MEB has granted a marketing authorisation for Beclometasondipropionaat/formoterolfumaraatdihydraat 100/6 microgram/dose and 200/6 microgram/dose Vincion, aërosol, solution, from Vincion B.V.

The product is indicated for:
Severe chronic obstructive pulmonary disease (COPD) (only 100/6 microgram/dose strength)

- the symptomatic treatment of patients with severe COPD (FEV_1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Asthma (both 100/6 microgram/dose and 200/6 microgram/dose strengths)

- the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta2-agonist) is appropriate:
  - patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting beta-2 agonist,
  - patients already adequately controlled with both inhaled corticosteroids and long-acting beta-2 agonists.

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. Bioequivalence cannot be demonstrated through bioavailability studies but therapeutical equivalence has been investigated by comparison of the delivered dose uniformity, aerodynamic particle size distribution and other parameters like spray pattern and impact of cleaning in line with the EMA clinical orally inhaled products (OIP) Guideline section 5.2 (CHMP/EWP/4151/ 00 Rev 1 January 2009) for the product as such (without spacer) and if used with the Aerochamber Plus spacer device (deep breathing, 2 seconds delay, and tidal breathing pattern). Use of this spacer is also described in the SmPC of the reference product.

In this national procedure, therapeutic equivalence is proven between the new product and the innovator product is Foster 100/6 microgram/dose, aerosol, solution (NL RVG 34610) which has been registered in the Netherlands by Chiesi Pharmaceuticals B.V. since 21 August 2007 by the mutual recognition procedure DE/H/0871/001.

II. QUALITY ASPECTS

II.1 Introduction

Beclometasondipropionaat/formoterolfumaraatdihydraat Vincion is an aërosol, solution. The solution is colourless to yellowish.

100/6 microgram/dose strength
Each dose contains as active substances 100 microgram beclometasone dipropionate and 6 microgram formoterol fumarate dihydrate per inhalation dosage. This is equivalent to a released dose (from the actuator) of 84.6 microgram beclometasone dipropionate and 5 microgram formoterol fumarate dihydrate.

200/6 microgram/dose strength
Each metered dose (from the dosing valve) contains as active substance 200 microgram beclometasone dipropionate and 6 microgram formoterol fumarate dihydrate. This is equivalent to a released dose (from the actuator) of 177.7 microgram beclometasone dipropionate and 5.1 microgram formoterol fumarate dihydrate.

The excipients are: norflurane (HFA-134a), anhydrous ethanol and hydrochloric acid (E507).

The aërosol, solution is packed under pressure in an aluminium canister, which is sealed with a metering valve and fits into a polypropylene plastic actuator consisting of a dose counter and a mouthpiece, and is equipped with a polypropylene protective cap. Each pack contains one or two spray canisters, which each provide 120 actuations.

II.2 Drug Substance

The active substances are beclometasone dipropionate and formoterol fumarate dihydrate.

Beclometasone dipropionate
Beclometasone dipropionate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder and is practically insoluble in water, freely soluble in acetone and sparingly soluble in ethanol (96%).

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. with additional requirements for residual solvents conform the CEP and additional residual solvents and microbial enumeration

conform Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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

Formoterol fumarate dihydrate
Formoterol fumarate dihydrate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white or slightly yellow powder and is slightly soluble in water and in 2-propanol, soluble in methanol and practically insoluble in acetonitrile.

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. with additional requirements for palladium and residual solvents conform the CEP and additional tests on residue on ignition, microbial enumeration and fumaric acid content. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained.

The objective was to develop a pressurised inhalation solution drug product which is qualitatively and quantitatively similar to the currently marketed reference product. The active ingredients and excipients are qualitatively and quantitatively the same as the

reference product. Besides the regular formulation and manufacturing process development studies, also specific development studies for inhalation products have been performed in line with EMA guideline on the pharmaceutical quality of inhalation and nasal products. The pharmaceutical development of the product is adequately performed.

Manufacturing process

The manufacturing process comprises dissolution of the active substance in the excipients in dedicated equipment, homogenising and subsequent filling into aluminium canisters and crimped. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. or Committee for Proprietary Medicinal Products (CPMP) 1994 (for norflurane) 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 description (bulk, formulation and pack), identification, total can content, uniformity of delivered dose of both active substances, fine particle mass of both active substances, moisture content, related substances of both active substances, leak rate, number of deliveries per container, mean delivered dose of both active substances, microbiological quality, colour index and alcohol content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

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

Stability of drug product

Stability data on the product have been provided for three batches stored at 2-8°C (21 months) and 25°C/60% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies in line with ICH have been performed as part of the forced degradation but are not relevant as the drug product is stored in aluminium canisters. On basis of the data submitted, a shelf life was granted of 21 months. The labelled storage conditions are “Before use: store in the refrigerator (2-8°C). And after first use: store below 25°C for maximum 3 months.”

In-use stability data have been provided demonstrating that the product remains stable for 3 months following first opening of the container, when stored at 25°C/60% RH.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Beclometasondipropionaat/formoterolfumaraatdihydraat Vincion 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)

At the time of submission of this application, before 1st of September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. At the time of approval the conclusion for this medicinal product was: since Beclometasondipropionaat/ formoterolfumaraatdihydraat Vincion 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 Foster which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Beclometasone dipropionate and formoterol fumarate dihydrate are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate

additional clinical data. Therefore, the MEB agreed that no further clinical studies are required.

IV.2 Pharmacokinetics, clinical efficacy and safety

To support this application, the MAH provided quality data and *in-vitro* data as per the EMA guideline for OIP (CPMP/EWP/4151/00 Rev.1). Consequently, no clinical studies were conducted. This is acceptable since therapeutical equivalence is established based on *in-vitro* quality data. The product will be authorised for the use in adults only.

IV.3 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 Beclometasondipropionaat/formoterolfumaraatdihydraat Vincion. At the time of approval, the most recent version of the RMP was version 2.0 dated 1 November 2022.

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

Important identified risks	• Changes in the electrocardiogram (ECG QTc prolongation)/ Heart problems such as an unusual fast heart beat and disorders of heart rhythm (tachycardia / tachyarrhythmia) • Infection of the lungs (pneumonia)
Important potential risks	• Growth retardation in children and adolescents when used off-label
Missing information	• Use in pregnancy and breastfeeding • Safety in children aged 5-11 and in adolescents aged 12-17 with asthma when used off-label

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

IV.4 Discussion on the clinical aspects

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

V. USER CONSULTATION

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 Foster 100/6 microgram/dose, aerosol, solution, DE/H/0871/001 (for content) and to several other medicinal product from Vincion for in-house design and layout. 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

Beclometasondipropionaat/formoterolfumaraatdihydraat 100/6 microgram/dose and 200/6 microgram/dose Vincion, aërosol, solution have a proven chemical-pharmaceutical quality and are hybrid forms of Foster 100/6 microgram/dose, aerosol, solution. Foster is a well-known medicinal product with an established favourable efficacy and safety profile.

In the second round assessment, a 'Major Objection' (MO) was raised as therapeutic equivalence was not adequately demonstrated based on *in-vitro* data. With the responses, the MAH provided data to demonstrate *in-vitro* equivalence between the test and reference product batches by leaving out the United Kingdom reference product batch from the calculations as requested. The re-calculated data show that *in-vitro* equivalence between the batches of test and reference products has been adequately demonstrated. Consequently, the MO is considered resolved. In addition, the MAH has tightened the limit on ethanol content as requested (and provided the analytical method validation report and an overview of the stability data), corrected the CEP version in the dossier and amended the storage conditions in the SmPC in line with the dossier. Therefore, the remaining 'Other Concerns' are also considered resolved.

Therapeutic equivalence has been shown to be in compliance with the requirements of European guidance documents. *In vitro* studies were performed to demonstrate therapeutic equivalence between Beclometasondiproprionaat /formoterolfumaraatdihydraat Vincion and the innovator product Foster in accordance with the OIP guidance document (i.e, CPMP/EWP/4151/00 rev.1 "*Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents*").

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that therapeutic equivalence has been demonstrated for Beclometasondipropionaat/formoterolfumaraatdihydraat Vincion with the reference product, and have therefore granted a marketing authorisation.

The national procedure was finalised with a positive outcome on 10 November 2023.

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
Type IA: B.II.b.3.z	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product - Other variation.	No	03-07-2024	Approved	N/A
Type IB: B.II.b.3.z	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product - Other variation.	No	05-08-2024	Approved	N/A
Type IA: B.III.1.a.2	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent /intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph	No	04-09-2024	Approved	N/A

	- Updated certificate from an already approved manufacturer.				
Art.61.(3)	Update of national PIL, label text and mock-ups: update fluorinated greenhouse gases.	Yes	04-11-2024	Approved	N/A
Type IA: B.II.e.2.a; Type IA: B.II.e.6.b	Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits. Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) - Change that does not affect the product information.	No	11-03-2025	Approved	N/A
Type IB: B.II.d.2.a	Change in test procedure for the finished product - Minor changes to an approved test procedure.	No	29-04-2025	Approved	N/A
Type IB: A.5.a	Change in the name and/or address of a manufacturer/	Yes	06-11-2025	Approved	N/A

	importer of the finished product (including batch release or quality control testing sites) - Manufacturer responsible for batch release.				