COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ciclesonide Sandoz Inhalator 80 and 160 microgram/actuation pressurised inhalation, solution
(ciclesonide)

NL/H/5651/001-002/DC

Date: 28 July 2026

This module reflects the scientific discussion for the approval of Ciclesonide Sandoz Inhalator 80 and 160 microgram/actuation pressurised inhalation, solution. The procedure was finalised on 22 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
DDU	Delivered Dose Uniformity
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
MDD	Mean Delivered Dose
Ph.Eur.	European Pharmacopoeia
pMDI	Pressurised Inhalation Solution Drug Product
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 Member States have granted a marketing authorisation for Ciclesonide Sandoz Inhalator 80 and 160 microgram/actuation pressurised inhalation, solution, from Sandoz B.V.

The product is indicated for: treatment to control persistent asthma in adults and adolescents (12 years and older).

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. The proposed products contain per metered dose the same amount of the same active substance and concern the same pharmaceutical form (pressurised inhalation, solution) as the innovator.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Alvesco Inhalator 80 µg/dose and 160 µg/dose, pressurised inhalation (NL RVG 31632 and RVG 31633) which has been registered in Sweden by Covis Pharma Europe B.V. since 2008 (transferred from the UK). In the Netherlands, Alvesco Inhalator has been registered since 2005.

The concerned member states (CMS) involved in this procedure were Denmark, Finland, Norway and Sweden.

The application refers to a medical device within the meaning of Article 2(2) of regulation (EU) 2017/745; medical device intended to administer a medicinal product where they form a single integral product which is intended exclusively for use in the given combination and which is not reusable. The MAH claimed that the device is Class I and the manufacturer's EU declaration of conformity does not require involvement of a notified body in the conformity assessment.

II. QUALITY ASPECTS

II.1 Introduction

Ciclesonide Sandoz Inhalator is a clear and colourless solution. Per 1 actuation (delivered dose from the mouthpiece) it contains 80 or 160 micrograms of ciclesonide. The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with green (80 microgram/actuation) or purple (160 microgram/actuation) dust cap.

The excipients are: norflurane (HFA-134a) and anhydrous ethanol.

The solution is packed in an inhaler. The inhaler comprises a pressurised container made from aluminium and is sealed with a metering valve, mouthpiece, and green dust cap (80 micrograms) or purple dust cap (160 micrograms).

II.2 Drug Substance

The active substance is ciclesonide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or yellowish-white, crystalline powder, practically insoluble in water, freely soluble to soluble in acetone and in anhydrous ethanol. Being a solution formulation, the particle size and the polymorphic form of the active substance are not critical.

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 acetic acid, residual solvents of which ethanol is in line with the CEP, particle size distribution (PSD) and microbiological enumeration. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
A re-test period of 60 months is stated for the active substance 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 objective was to develop a pressurised inhalation solution drug product (pMDI) which is qualitatively and quantitatively similar to the currently marketed reference product. The proposed 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.

No bioequivalence study was performed but therapeutical equivalence has been investigated solely based on comparative *in vitro* data by comparison of the delivered dose uniformity (DDU), mean delivered dose (MDD), aerodynamic particle size distribution and other parameters like spray pattern, water content and impact of cleaning in line with the EMA clinical 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 Flow Vu spacer device (tidal breathing pattern, 500 ml volume, 2 seconds delay) before and after cleaning. Use of this spacer is also described in the SPC of the reference product. For the UDD/MDD a dosage unit sampling apparatus was used at a flow of 28.3 l/min in line with Ph.Eur. 0671. For APSD the Next Generation Impactor (NGI) was used at a flow of 30 ml/min. The comparative aerodynamic particles size distribution (APSD) data have been analysed for the individual stages in accordance with the Final OIP Guideline CPMP/EWP/4151/00 Rev.1, to investigate whether the 90% Confidence Intervals (CIs) for the ratio of the log transformed Test and Reference means (T/R) fall within the suggested ± 15% *in vitro* limits. It should be noted that the upper limit of 118% is applied for 90% upper CI of geometric mean ratio throughout the dossier. Based on the results therapeutical equivalence has been adequately demonstrated.
Also dose proportionality has been demonstrated with and without add on device by evaluation of the APSD results using the NGI at 30 l/min. using two literature approaches (Garcia-Arieta and Power Law analysis) and grouping of stages. The applied grouping of stages has been adequately justified.

Manufacturing process

The manufacture of pMDIs is considered a non-standard but usual manufacturing process. The manufacturing 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. requirements. Norflurane also complies with the more stringent IPACT1 specifications. 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, appearance and colour, number of actuations per canister, ciclesonide identification and assay, related substances, MDD and UDD (both intra-can and inter-can), moisture content, ethanol identification and content, aerodynamic particle size distribution/free particulate matter (APSD/FPM), leak rate, microbiological quality and leachables. 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 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 full scale batches per strength stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of three years. No specific storage conditions needed to be included in the SmPC or on the label.

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 member states consider that Ciclesonide Sandoz Inhalator has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ciclesonide Sandoz Inhalator is intended for generic 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 Alvesco Inhalator 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cicleosonide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on *in vitro* and scientific literature data. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ciclesonide Sandoz Inhalator. At the time of approval, the most recent version of the RMP was version 1.0 dated 26 July 2022.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the *in vitro* clinical data and experience with the innovator product Alvesco Inhalator. 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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Alvesco Inhalator 80 µg/dose and 160 µg/dose, pressurised inhalation, SE/H/1861. The bridging report submitted by the MAH has been found acceptable; bridging is justified for content. The layout is identical to the MAH's house style, which has been already accepted previously, and is therefore acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ciclesonide Sandoz Inhalator 80 and 160 microgram/actuation pressurised inhalation, solution have a proven chemical-pharmaceutical quality and are hybrid forms of Alvesco Inhalator 80 µg/dose and 160 µg/dose, pressurised inhalation. Alvesco is a well-known medicinal product with an established favourable efficacy and safety profile.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered therapeutic equivalence has been demonstrated for Ciclesonide Sandoz Inhalator with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 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
NL/H/5651/001-2/IA/001/G	Change in the name and/or address of the marketing authorisation holder	Yes	8-8-2024	Approved	N/A
NL/H/5651/001-2/IB/002	Change in test procedure for the finished product • Other changes to a test procedure (including replacement or addition)	No	9-10-2024	Approved	N/A
NL/H/5651/001-2/P/001	Art.61(3): Providing information on fluorinated gases	Yes	18-2-2025	Approved	N/A