COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Montelukast OPKO 10 mg tablets (montelukast sodium)

NL/H/5645/001/DC

Date: 9 March 2026

This module reflects the scientific discussion for the approval of Montelukast OPKO 10 mg tablets. The procedure was finalised on 13 June 2024. 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
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
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 Member States have granted a marketing authorisation for Montelukast OPKO 10 mg tablets, from OPKO Health Spain S.L.U.

The product is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β -agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast OPKO is indicated in asthma, Montelukast OPKO can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast OPKO is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

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(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Singulair 10 mg film-coated tablets (FI/H/0104/001) which has been registered in the Netherlands by N.V. Organon since 3 November 1998 (NL RVG 23164).

The concerned member state (CMS) involved in this procedure was Spain.

II. QUALITY ASPECTS

II.1 Introduction

Montelukast OPKO is an uncoated, round, biconvex, light brown tablet, with a breakline on both sides.
The breaklines are only to facilitate breaking for ease of swallowing and not to divide into equal doses.

One tablet contains as active substance montelukast sodium, which is equivalent to 10 mg montelukast.

The excipients are: mannitol (E421), microcrystalline cellulose (E460i), croscarmellose sodium (E468), aspartame (E951), cherry flavouring, iron oxide red (E172), iron oxide yellow (E172) and magnesium stearate (E470b).

The tablets are packed in Aluminium (ALU)/Aluminium (ALU) blisters.

II.2 Drug Substance

The active substance is montelukast sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water and methylene chloride, freely soluble to very soluble in ethanol (96%). The amorphous form of Montelukast sodium is used.

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 tests, mentioned by the CEP, for two residual solvents. Furthermore, additional tests for microbial quality and particle size distribution are included in the drug substance specification from the drug product manufacturer. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for four years 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 explained. The choices of the packaging and manufacturing process are discussed.

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 production scale batches per batch size (small, medium and large) in accordance with the relevant European guidelines.

Control of excipients

Almost the same excipients are used as in the reference product Singulair 10 mg. The excipients comply with the Ph.Eur. or United States Pharmacopeia and National Formulary (USP-NF) except for the cherry flavour which comply with in-house requirements. Adequate justification is provided for the specifications of the excipients, including functionality related characteristics. 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, identification, uniformity of dosage units, dissolution, assay, average weight, water content, subdivision of tablets, related substances and microbial limits. 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 nine production 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 ten full scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed and it was concluded that the drug product is photosensitive. On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are: “This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.”

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 Montelukast OPKO 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 Montelukast OPKO 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 generic formulation of Singulair 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

Montelukast is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Montelukast OPKO 10 mg tablets (OPKO Health Spain S.L.U., Spain) was compared with the pharmacokinetic profile of the reference product Singulair 10 mg film-coated tablets (N.V. Organon, the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Comparative dissolution profiles for the test and reference products at different levels of pH (1.2, 4.5, 6.8 and QC conditions) with and without a surfactant have been provided, confirming that both products are similar with respect to dissolution. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study

Design

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-27 years. Each subject received a single dose (10 mg) of one of the two montelukast formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14 and 24 hours after administration of the products.

The design of the study is acceptable.

Montelukast may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of montelukast. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects did not want to continue the trial after dosing in the first period of the trial and therefore did not provide any samples. Two other subjects were excluded from the statistical analysis due to vomiting within 6 hours post-dose, which noticeably affected the concentration-time profile. Of the 28 subjects enrolled in the study, 24 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of montelukast, 10 mg under fasted conditions.

Treatment N=24	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	3531 ± 763	3641 ± 799	566 ± 117	2.75 (2.00 – 5.00)
Reference	3269 ± 889	3371 ± 919	509 ± 149	3.00 (1.50 – 5.50)
***Ratio (90% CI)**	1.09 (1.02 – 1.17)	-	1.12 (1.03 – 1.22)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Montelukast OPKO is considered bioequivalent with Singulair.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Montelukast OPKO. At the time of approval, the most recent version of the RMP was version 1.0 dated 7 October 2022.

Table 2. 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.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Singulair. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product

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 Singulair 10 mg comprimidos recubiertos con película, FI/H/0104/001 (for key safety messages) and to Soluzem 2 mg cápsulas duras, DK/H/3350/001/DC (for leaflet 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

Montelukast OPKO 10 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Singulair 10 mg film-coated tablets. Singulair is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 that essential similarity has been demonstrated for Montelukast OPKO with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 June 2024.

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/5645/001 /IA/001	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 - Updated certificate from an already approved manufacturer.	No	19-8-2025	Approved	N.A.
NL/H/5645/001 /IA/002/G	Change in test procedure for active substance or starting material/reagent /intermediate used in the manufacturing process of the active substance - Minor changes to an approved test procedure. Change to comply with Ph. Eur. or with a national pharmacopoeia	No No	14-10-2025	Approved	N.A.

	of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State.				