IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Montelukast Pinewood 4mg Chewable Tablets
Montelukast sodium
PA0281/261/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety, and efficacy, the HPRA has granted a marketing authorisation for Montelukast Pinewood 4 mg & 5 mg Chewable Tablets and Montelukast Pinewood 10 mg Tablets, from Pinewood Laboratories Ltd on 28th June 2024 for the following indications:

For Montelukast Pinewood 4mg and 5 mg Chewable Tablet 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;
- as an alternative treatment option to low-dose inhaled corticosteroids for patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids;
- in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

For Montelukast Pinewood 10 mg Tablet, 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 Sodium Pinewood 10 mg tablet is indicated in asthma, Montelukast Sodium Pinewood 10 mg tablet can also provide symptomatic relief of seasonal allergic rhinitis;
- in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

This application was made referring to Article 10.1 "generic application" of Directive 2001/83/EC, as amended. With Ireland as the Reference Member State (RMS) in this decentralised procedure, Pinewood Laboratories Limited applied for the Marketing Authorisations for Montelukast Pinewood 4 mg & 5 mg Chewable Tablets and Montelukast Pinewood 10 mg Tablets in Concerned Member State (CMS) Malta.

The reference products stated on the application form for the purpose of data exclusivity and product information were Singulair Paediatric 4 mg chewable tablets (PA23198/014/001), Singulair Paediatric 5 mg chewable tablets (PA23198/014/003) and Singulair 10mg film-coated tablets (PA23198/014/004), respectively, by Organon Pharma (Ireland) Limited, registered since 20/02/1998 in Ireland.

In support of this application, the applicant submitted data from two bioequivalence studies.

Montelukast Pinewood 4 mg & 5 mg Chewable Tablets and Montelukast Pinewood 10 mg Tablets were authorised as medicinal products subject to prescription that may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Montelukast Pinewood 4mg Chewable Tablets
Name(s) of the active substance(s) (INN)	Montelukast sodium
Pharmacotherapeutic classification (ATC Code)	R03DC03
Pharmaceutical form and strength(s)	4mg Chewable Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/261/001
Marketing Authorisation Holder	Pinewood Laboratories Ltd Ballymacarbry Clonmel Co. Tipperary Ireland
MRP/DCP No.	IE/H/1213/001
Reference Member State	IE
Concerned Member State(s)	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Montelukast Pinewood 4 mg & 5 mg Chewable Tablets and Montelukast Pinewood 10 mg Tablets.

II.2 Drug substance

The active substance is Montelukast sodium an established active substance described in the European/British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

One chewable tablet contains montelukast sodium, which is equivalent to 4 mg or 5 mg montelukast.
One tablet contains montelukast sodium, which is equivalent to 10 mg montelukast.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established/a novel pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Montelukast Pinewood 4 mg & 5 mg Chewable Tablets and Montelukast Pinewood 10 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Singulair on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of Montelukast are well known.

III.2 Ecotoxicity/environmental risk assessment

Since Montelukast Sodium Pinewood 4 mg and 5 mg Chewable Tablet and Montelukast Sodium Pinewood 10 mg Tablet is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

As Montelukast is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy, and safety of montelukast are well-known. With the exception of data from two bioequivalence studies, no new clinical data were provided or are required for this type of application.

The two submitted bioequivalence studies are discussed in section IV.2 below.

A biowaiver was sought and granted for the lowest strength (4 mg) on the basis of data from the two clinical studies and additional supporting data.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

The content of the SmPCs approved during the decentralised procedure are in accordance with those accepted for the cited reference products.

IV.2 Pharmacokinetics

The applicant submitted two bioequivalence studies in support of this application:

- Study 411-TP-07-02-0000 was an open label, randomized, cross over, single dose, bioequivalence study of two oral preparations Montelukast 5 mg chewable tablets, (Test: Finished product manufacturer, India) vs. Singulair Junior® 5 mg Kautabletten, (Reference: MSD Dieckmann Arzneimittel GmbH, Germany) in healthy volunteers in the fed state.
- Study 411-TP-07-01-0000 was an open label, randomized, cross over, single dose, bioequivalence study of two oral preparations Montelukast 10 mg tablets, (Test: Finished product manufacturer, India) vs. Singulair® 10 mg

Filmtabletten, (Reference: MSD Dieckmann Arzneimittel GmbH, Germany) in healthy volunteers in the fastened state.

Based on data submitted from Study 411-TP-07-02-0000, Montelukast 5mg tablet was demonstrated to be bioequivalent to Singulair Junior® 5 mg Kautabletten in the fed state. A summary of data is presented below:

Bioequivalence analysis for montelukast (N=25):

Pharmacokinetic Parameter [N=25]	Point estimate	Confidence Intervals***	ANOVA-log CV(%)
AUC(0-tlast) (ratio test/reference)	0.985*	0.923 - 1.051*	13.40%
Cmax (ratio test/reference)	1.005*	0.942 -1.073*	13.44 %

Based on data submitted from Study 411-TP-07-01-0000, Montelukast 10 mg tablet, was demonstrated to be bioequivalent to Singulair 10 mg tablet. A summary of data is presented below:

Bioequivalence analysis for montelukast (N=24):

PK Parameters	90% Confidence Interval (Lower limit-Upper limit)	Test value (test/reference)	Intra Subject CV% *
Cmax	1.025-1.223	1.092	17.64
AUC(0-t)	1.021-1.167	1.119	13.28

Supportive comparative in-vitro dissolution data were presented for the test Montelukast 5 mg and 10 mg products against the reference products, Singulair 5 mg and 10 mg products, respectively, in line with CHMP guidance.

A biowaiver for the test Montelukast 4 mg chewable tablet was requested by the applicant on the basis of reported demonstration of bioequivalence between the 5 mg test and reference products. The general biowaiver criteria, as per CHMP guidance, were fulfilled, and the proposed biowaiver was granted.

IV.3 Pharmacodynamics

No new data were submitted or required.

IV.4 Clinical Efficacy

No new data have been submitted and none are required. The reference product is established, and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of montelukast is well-established from its extensive use in clinical practice.

IV.5 Clinical Safety

Montelukast sodium has an acceptable adverse event profile. No new safety concerns arose in the submitted bioequivalence studies.

A risk management plan was submitted, 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 Sodium Pinewood 4mg and 5mg chewable tablets and Montelukast Sodium Pinewood 10mg tablets. The submitted Risk Management Plan is considered acceptable.

Periodic Safety Update Reports (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.

IV.6 Discussion on the clinical aspects

Data from the two clinical bioequivalence studies (for the 10 mg and 5 mg strength) and in vitro data submitted in support of the biowaiver request for the third strength (4 mg) have satisfactorily established bioequivalence between the test products of the applicant and the reference medicinal products.

The clinical overview is based on published literature data. This is acceptable since montelukast is a well-known active substance and essential similarity is claimed to the reference product. This is considered sufficient for this type of application.

V. OVERALL CONCLUSIONS

Montelukast Pinewood 4 mg & 5 mg Chewable Tablets and Montelukast Pinewood 10 mg Tablets, from Pinewood Laboratories Ltd, are generic forms of Singulair Paediatric 4 mg chewable tablets, Singulair Paediatric 5 mg chewable tablets, and Singulair 10mg film-coated tablets, respectively, by Organon Pharma (Ireland) Limited. Singulair is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with guidance documents. The SmPCs are consistent with those of the reference products.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of data submitted considered that Montelukast Pinewood 4 mg & 5 mg Chewable Tablets and Montelukast Pinewood 10 mg Tablets, from Pinewood Laboratories Ltd, demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted marketing authorisations to all three product strengths.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New DCP as RMS	IE/H/1213/001-003/DC	SmPC, PIL, IPAR		