CBG MEB

Public Assessment Report

Scientific discussion

Mooncast 4 mg and 5 mg, chewable tablets

(montelukast sodium)

NL License RVG: 113175 and 113177

Date: 7 March 2019

This module reflects the scientific discussion for the approval of Mooncast 4 mg and 5 mg, chewable tablets. The marketing authorisation was granted on 15 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
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
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Mooncast 4 mg and 5 mg, chewable tablets from Maddox Pharma Swiss B.V.

The product is indicated for:

- treatment of asthma as combination therapy in patients aged 2-5 years old 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.
- an alternative treatment option to low-dose inhaled corticosteroids for patients aged 2-5 years old 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.
- prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction in patients aged 2 years and older.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator products Singulair 4 mg and 5 mg chewable tablets which have been registered in Finland by MSD since 1997. In the Netherlands, Singulair 5 mg chewable tablets (NL License RVG 23165) has been registered since 1998 by the procedure FI/H/0104/002/MR, and the authorisation for Singulair 4 mg (NL License RVG 25800) was recognised through a mutual recognition procedure in 2001 (FI/H/0104/003). In addition, reference is made to Singulair authorisations in the individual member states.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Mooncast is a pink, mottled, oval, biconvex chewable tablet with "M4" or "M5" engraved on one side and containing as active substance 4 mg or 5 mg of montelukast.

The chewable tablets are packed in OPA-Al-PVC/Al blisters.

The excipients are: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, mannitol, aspartame (E951) and magnesium stearate.

Pigment blend – lactose monohydrate and red iron oxide (E172)
Silarom cherry flavour – nature-identical flavouring substances, flavouring preparations, natural flavouring substances, maltodextrin (potato), Arabic gum (acacia) (E414), triacetin (E1518), ethyl maltol, maltol and alfa-tocopherol (E307)

The 4 mg and 5 mg strengths are fully dose proportional.

II.2 Drug Substance

The active substance is montelukast sodium, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). Montelukast sodium is a white to off white to light yellow amorphous powder. It is freely soluble in methanol, ethanol and water and practically insoluble in acetonitrile. Montelukast sodium has one asymmetric centre and is the R-isomer. The amorphous form is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The MAH sources the substance from two manufacturers. The manufacturing process is described in sufficient detail. Starting materials are accepted.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches from the second manufacturer.

Stability of drug substance
Two batches from the first manufacturer have been stored at 25°C/60% RH and at 40°C/75% RH for 6 months in the proposed market packaging. No significant changes over the 6 months of testing at either condition. A retest period of 12 months with no special storage precautions is proposed and can be accepted.

Three commercial scale process validation batches from the second manufacturer have been stored at 25°C/60% RH for 9 months and at 40°C/75% RH for 6 months in the proposed market packaging. No significant changes were shown over the time period of testing at either condition. A retest period of 18 months with no special storage precautions is proposed and can be accepted.

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. In general, the pharmaceutical development for this national application is identical to Montelukast Actavis 4 mg and 5 mg chewable tablets, an already approved product in the Netherlands (NL License RVG 104210 and 104214).

One bioequivalence study was submitted with the 5 mg strength against Singulair 5 mg chewable tablets. The composition of the test batch was identical to the proposed market product.
The MAH has demonstrated similarity in dissolution between the 5 mg versus the 4 mg strength of drug product in pH 1.2, 4.5 and 6.8 dissolution media with and without surfactant being present. Overall, the data show a rapid and relatively pH independent release profile with >85% dissolved across the pH range within 15 minutes.

Manufacturing process
The manufacturing process is considered a non-standard manufacturing process (containing <2% of active ingredient). The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with Ph.Eur. except Silarom Cherry Flavour and Pigment Blend. Qualitative compositions are provided for both non-pharmacopoeial excipients, together with brief specifications. This is 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, friability, resistance to crushing, dissolution, average tablet mass, uniformity of dosage units, related substances, assay and

microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two batches of each strength 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 pilot scale batches per strength. Two were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Third batch was stored at 30°C/75% RH (24 months) and 40°C/75% RH (6 months). Out of specification results for a specified impurity were seen for one batch after 6 months storage at 40°C/75% RH and for the same batch after 24 months storage at 30°C/75% RH. Other than that, no clear trends or changes were seen in any of the tested parameters at all three storage conditions. Based on the available stability data the claimed shelf-life of 36 months with storage condition "Store in the original package in order to protect from light and moisture. Do not store above 30°C." is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate (present in the pigment blend) is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Mooncast 4 mg and 5 mg, chewable tablets 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 Mooncast 4 mg and 5 mg, chewable tablets 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Singulair which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Montelukast sodium is a well-known active substance 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 agrees that no further clinical studies are required.

For this generic application, the MAH has submitted 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 Mooncast 5 mg, chewable tablets (Maddox Pharma Swiss B.V, The Netherlands) is compared with the pharmacokinetic profile of the reference product Singulair Junior 5 mg chewable tablets (MSD Dieckmann Arzneimittel GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The results of this 5 mg study can be extrapolated to the 4 mg strength based on the following:

- The products are manufactured by the same manufacturer and process
- The qualitative composition of the different strengths is the same
- The ratio between amounts of active substance and excipients is the same
- The dissolution profiles are similar in three different pH conditions for the additional strength.
- Montelukast kinetics were reported to be linear over the dose range

Bioequivalence study
Design
A randomised cross-over bioequivalence study was carried out under fasted conditions in 36 healthy male subjects. Each subject received a single dose (5 mg) of one of the two montelukast formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of nine days.

Blood samples were collected pre-dose and at and at 0.5, 0.75, 1, 1.333, 1.667, 2, 2.25, 2.5, 2.75, 3, 3.333, 3.667, 4, 4.333, 4.667, 5, 5.5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable.

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
One subject was withdrawn due to a rash. Therefore 35 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1742.49 ± 409.38	1795.33 ± 434.47	334.37 ± 60.37	2.710	5.10 (0.74)
Reference	1710.80 ± 461.98	1771.36 ± 496.00	306.45 ± 84.80	2.798	5.22 (1.01)
***Ratio (90% CI)**	1.00 (0.99 – 1.06)	1.02 (0.99 – 1.06)	1.12 (1.04 – 1.19)	-0.25 (0.58 – 0.33)	
CV (%)	8.35	8.44	16.65		

$AUC_{0-\infty}$	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 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ln-transformed values*

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

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 Mooncast.

Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	• Depression in paediatric patients • Suicidality in paediatric patients
Missing information	None

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 Singulair chewable tablets. No new clinical studies were conducted. 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

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. The test consisted of: a pilot test with three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mooncast 4 mg and 5 mg, chewable tablets has a proven chemical-pharmaceutical quality and is a generic form of Singulair 4 mg and 5 mg chewable 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Mooncast with the reference product, and have therefore granted a marketing authorisation. Mooncast 4 mg and 5 mg, chewable tablets was authorised in the Netherlands on 15 January 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Product information update	Type IAin: B.II.b.2.c.1	18-03-2015	14-04-2015	Non-approval	N
Product information update	Type IAin: B.II.b.2.c.1	01-06-2015	27-07-2015	Approval	N
Product information update	Type IAin: B.III.1.a.1	22-01-2016	01-02-2016	Approval	N
Transfer of MAH from Medcell Pharma B.V. to Meren Pharma B.V.	Type IB: A.2.b	18-03-2016	20-04-2016	Approval	N
Product information update	Type IAin: A.1; Type IB: A.2.b	16-02-2017	07-04-2017	Approval	N
Product name change	Type IB: A.2.b	03-05-2017	20-06-2017	Approval	N
Product information update	Type IAin: A.1	25-05-2018	24-06-2018	Approval	N
Product information update	Type IB: C.I.2.a	4-06-2018	17-07-2018	Approval	N