CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lukastang 4 mg and 5 mg, chewable tablets
Lukastang 10 mg, film-coated tablets
M.R. Pharma GmbH, Germany

montelukast (as sodium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1724/001-003/DC
Registration number in the Netherlands: RVG 105131-105133

27 January 2011

Pharmacotherapeutic group:	other systemic drugs for obstructive airway diseases; leukotriene receptor antagonists
ATC code:	R03DC03
Route of administration:	oral
Therapeutic indication:	treatment of mild to moderate persistent asthma as add-on therapy; alternative treatment option to low-dose inhaled corticosteroids (4/5 mg only); prophylaxis of asthma when the predominant component is exercise-induced bronchoconstriction; symptomatic relief of seasonal allergic rhinitis (10 mg only)
Prescription status:	prescription only
Date of authorisation in NL:	13 January 2011
Concerned Member States:	Decentralised procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Lukastang 4 mg and 5 mg, chewable tablets and Lukastang 10 mg, film-coated tablets from M.R. Pharma GmbH. The date of authorisation was on 13 January 2011 in the Netherlands.

The product is indicated for:

- 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.
- (4 and 5 mg only) 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.
- prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

The 4 mg chewable tablet is indicated for children aged 2 to 5 years old, the 5 mg tablet for children and adolescents 6-14 years of age, and the 10 mg film-coated tablet for patients from 15 years of age.
In those asthmatic patients in whom montelukast 10 mg, film-coated tablets is indicated in asthma, it can also provide symptomatic relief of seasonal allergic rhinitis.

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

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important proasthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.
Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within two hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and paediatric patients, 2 to 14 years of age, montelukast decreased peripheral blood eosinophils compared with placebo while improving clinical asthma control.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Singulair 10 mg film-coated tablets, Singulair 4 mg and 5 mg chewable tablets which have been registered in Finland by MSD since 1997. In the Netherlands, Singulair 10 mg film-coated tablets and Singulair 5 mg chewable tablets (NL License 23164-23165) have been registered since 1998 by the procedure FI/H/0104/001-002/MR, and the authorisation for Singulair 4 mg (NL RVG 25800) was recognised through MRP in 2001 (FI/H/0104/003). In addition, reference is made to Singulair authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the 5 mg and 10 mg test

products is compared with the pharmacokinetic profile of the reference products Singulair junior 5 mg chewable tablets and Singulair 10 mg film-coated tablets, both registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is montelukast sodium, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is an off-white, white to pale yellow amorphous, hygroscopic powder, which is soluble in methanol, ethanol and water, and practically insoluble in acetonitrile. Montelukast sodium has one asymmetric centre and is the R-isomer.

The Active Substance Master File (ASMF) procedure is used for all three suppliers of 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 manufacturing process is described for different batch sizes. Adequate specifications are applied for the starting materials, including limitation of the undesired S-enantiomer. Sufficient information has been provided on solvents and reagents. Absence of genotoxic impurities has been adequately demonstrated.

Quality control of drug substance
The specification for the active substance can be accepted in general and the analytical procedures are regarded suitable to control the quality of the drug substance. The specifications of the MAH apply to the drug substance of all suppliers. Certificates of analysis of three production-scale batches were submitted with acceptable results.

Stability of drug substance
Stability studies have been performed with the drug substance. No significant changes in any of the parameters were observed. The proposed retest periods are acceptable: 18 months for one supplier and 24 months for the other two manufacturers. Also the storage recommendation 'no temperature limitations' is regarded acceptable and justified by the outcome of the submitted stability studies.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Lukastang 4 mg is a pink, oval, biconvex-shaped tablet with 'M4' engraved on one side.
Lukastang 5 mg is a pink, round, biconvex-shaped tablet with 'M5' engraved on one side.
Lukastang 5 mg is a beige coloured, round, biconvex-shaped film-coated tablet.

The 4 and 5 mg tablets are fully dose proportional.

The tablets are packed in Nylon/Alu/PVC-Aluminium blisters or HDPE bottles with PP cap and desiccant.

The excipients are:
4 and 5 mg chewable tablets
microcrystalline cellulose, mannitol (E421), crospovidone (type B), red iron oxide (E172), hydroxypropylcellulose, disodium edetate, cherry flavour, aspartame (E951), talc, magnesium stearate.

10 mg film-coated tablets
Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, disodium edetate, magnesium stearate.
Film-coating: hypromellose, hydroxypropyl cellulose, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172).

Pharmaceutical development
The choice of excipients and packaging material has been sufficiently explained. The proposed products have been compared with originator products in different media. The batches used for the 5 mg and 10 mg dissolution studies are the ones used in the bioequivalence studies. The dissolution profiles are similar between the originator and the proposed products. For the 5 mg tablet and 10 mg tablet bioequivalence studies have been performed with the corresponding German reference products. This test product is acceptable, as the reference product is identical to the product registered in the Netherlands. The biowaiver for the 4 mg strength is acceptable from a chemical-pharmaceutical point of view. The pharmaceutical development has been sufficiently described and explained.

Manufacturing process
The drug products are manufactured in a wet granulation process. The process consists of blending, mixing, drying and sifting steps. Finally the blend is compressed into tablets. The 10 mg tablets are subsequently film-coated. The manufacturing process is considered non-standard as the amount of drug substance is less than 2.5%. Process validation data have been provided on full-scale batches from both manufacturing sites.

Control of excipients
Except for the cherry flavour, iron oxides and coating material Opadry yellow, where an in-house specification is provided, all excipients comply with their Ph.Eur. monograph. The safety and quality of the cherry flavour has been demonstrated. The specifications are acceptable.

Quality control of drug product
The finished product specification is in general regarded acceptable taking into account all important parameters of the product. The specification includes tests for description, identification, resistance to crushing, uniformity of dosage units, dissolution, related substances, assay, water and microbial limits. For the 10mg tablets an identification test for the iron oxides has been included.
All analytical methods have been adequately described and the quantitative methods have been adequately validated. Batch analysis results have been provided for four batches of both strengths of the chewable tablets and for six batches of the film-coated tablets demonstrating compliance with the release specifications.

Stability of drug product

The stability data of 36 months during storage at 25°C/40% RH demonstrate an increase in impurities and bacterial count and some variation for assay and dissolution, but no clear trend was observed. All parameters remain well within the set limits. For the other parameters no clear trends could be observed.
Photostability testing showed that the 4 mg and 5 mg tablets are sensitive to light, whereas the 10 mg product is photostable.
Based on the results for both the 4 and 5 mg chewable tablets and the 10 mg film-coated tablets, a shelf life of 3 years could be granted. No specific storage temperature is required. The chewable tablets should be stored in the original packaging to protect from light.

Several commitments have been made with regard to the finished product; these can be found on page 9 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A TSE certificate has been provided for lactose monohydrate, which is of bovine origin. Magnesium stearate is of vegetable origin, so a theoretical risk for TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Singulair, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of montelukast released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Montelukast is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Lukastang 5 mg chewable tablets and Lukastang 10 mg film-coated tablets (M.R. Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Singulair junior 5 mg chewable tablets and Singulair 10 mg film-coated tablets (MSD/Dieckman Arzneimittel GmbH, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – 5 mg chewable tablets
Design
A single-dose, laboratory-blind, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (17 females/19 males), aged 19-40 years. Each subject received a single dose (5 mg) of one of the 2 montelukast formulations. After overnight fasting for at least 10 hours, a single montelukast oral chewable tablet was chewed and subsequently the mouth was rinsed was with 200 ml of water. There were 2 dosing periods, separated by a washout period of 7 days.
Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

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
All subjects completed both study periods and passed all study procedures. Thirty-six subjects were included for plasma samples analyses according to the study protocol.

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

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1891 ± 654	1929 ± 659	275 ± 78	3.0 (1.0-5.0)	4.6 ±1.2
Reference	1911 ± 514	1950 ± 524	305 ± 67	2.0 (1.33-5.0)	4.6 ± 0.8
***Ratio (90% CI)**	0.97 (0.91-1.04)	0.97 (0.91-1.04)	0.89 (0.82-0.96)	--	--
CV (%)	16.7	16.6	19.5	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of montelukast under fasted conditions, it can be concluded that Lukastang 5 mg and Singulair junior 5 mg chewable tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation to 4 mg strength
A waiver for the 4 mg chewable tablets was granted, as all of the following conditions are fulfilled:
- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- 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 under identical conditions for both strengths.

<u>Bioequivalence study II – 10 mg film-coated tablets</u>
Design
A single-dose, open-label, laboratory-blind, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (18 females/18 males), aged 19-44 years. Each subject received a single dose (10 mg) of one of the 2 montelukast formulations. The tablet was orally administered with 200 ml of water after overnight fasting for at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.
Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, and 48 hours after administration of the products.

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 complete both study periods. One subject withdrew for personal reasons and another subject was withdrawn because of a positive pregnancy test before the second period. Thirty-four subjects were included for PK and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of montelukast under fasted conditions.

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3068 ± 1058	3112 ± 1068	458 ± 134	2.67 (1.50-6.00)	6.2 ± 3.2
Reference	3069 ± 1078	3125 ± 1085	456 ± 129	2.67 (1.00-6.00)	6.5 ± 2.7
***Ratio (90% CI)**	1.00 (0.94-1.07)	1.00 (0.93-1.07)	1.00 (0.93-1.08)	--	--
CV (%)	16.6	16.3	18.5	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of montelukast under fasted conditions, it can be concluded that Lukastang 10 mg and Singulair 10 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Montelukast should be taken without reference to food intake. From the literature it is known that food interacts with the absorption of montelukast. This is clearly stated in the SPC. 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.

The MEB has been assured that the bioequivalence studies have 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).

Risk management plan
Montelukast was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of montelukast can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are

sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC established during the decentralised procedure is in line with the SPC of the originator product, which was subject to an Article 30 referral in 2008.

Readability test
The package leaflet has not been evaluated via a user consultation study. As the product information is in full accordance with the innovator texts, no readability test was considered necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lukastang 4 mg and 5 mg, chewable tablets and Lukastang 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Singulair 4 mg and 5 mg chewable tablets and 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is in full accordance with that of the reference product, as established during the referral in 2008. The SPC, package leaflet and labelling are in the agreed templates.

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 Lukastang 4 mg and 5 mg, chewable tablets and Lukastang 10 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 April 2010. Lukastang 4 mg and 5 mg, chewable tablets and Lukastang 10 mg film-coated tablets were authorised in the Netherlands on 13 January 2011.

A European harmonised birth date has been allocated (25 August 1997) and subsequently the first data lock point for montelukast is September 2012. The first PSUR will cover the period from April 2010 to September 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: March 2013.

The following post-approval commitments have been made during the procedure:

<u>Quality - active substance</u>

- The MAH committed to fully validate the first three batches for all granulation batch sizes at each manufacturing site at which the product will be produced.
- The MAH committed to fully validate each potential tablet batch size that will be compressed out of the common granules from compression stage onwards (chewable tablets only).
- The MAH committed to perform long term and accelerated stability studies on the first three production scaled batches.
- The MAH committed to perform microbiological testing for the in-use stability with the drug product at the end of shelf-life.
- The MAH committed to provide stability data of each strength manufactured at different sites and stability data for the batches manufactured with the active substance from all the three API sources.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached