

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Montelukast Synthron 4 mg and 5 mg chewable tablets
Montelukast Synthron 10 mg film-coated tablets
Synthron B.V., the Netherlands**

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/2253/001-003/MR
Registration number in the Netherlands: RVG 108679-108681**

23 August 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; prophylaxis of asthma when the predominant component is exercise-induced bronchoconstriction.
Prescription status:	prescription only
Date of first authorisation in NL:	11 November 2010
Concerned Member States:	Mutual recognition procedure with DE, FR, SE, UK
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 Montelukast Synthron 4 mg and 5 mg chewable tablets and Montelukast Synthron 10 mg film-coated tablets, from Synthron B.V. The date of authorisation was on 11 November 2010 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.
- 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 (See section 4.2).
- prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

In the first two indications, the 4 mg tablet is indicated for children aged 2 to 5 years old, and when used for prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction, for children from 2 years of age and older. The 5 mg tablet is indicated for children and adolescents 6-14 years of age.

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

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) 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 CysLT₁ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD₄ 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 mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Singulair, which has been registered in Finland by MSD since 1997 (5 mg and 10 mg). In the Netherlands, Singulair 5 mg chewable tablets (NL License RVG 23165) has been registered since 1998 by the procedure FI/H/0104/001/MR, and the authorisation for Singulair 4 mg 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: one in which the pharmacokinetic profile of the product is

compared with the pharmacokinetic profile of the reference product Singulair junior 5 mg chewable tablets and one with Singulair 10 mg film-coated tablets as reference product. Both reference products were obtained from the German market. 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 a white to slightly yellow powder. Montelukast sodium is hygroscopic. No polymorphism is observed for the drug substance.

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 manufacturing process has been sufficiently described. Adequate specifications are applied for all starting materials.

Quality control of drug substance

In general reasonable and adequate drug substance specifications are applied. The MAH has set adequate limits for quality control of the drug substance. Batch analytical data have been submitted on three batches, demonstrating compliance with the specification. The MAH will consider tightening the limits in the drug substance specification in line with the Ph.Eur. when a monograph is available.

Stability of drug substance

During the 12 months normal and 6 months accelerated studies no changes or trends are observed, and all results meet the set requirements. Based on the available stability results and the results from the photostability study, the claimed re-test period of 1 year could be granted.

* *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

Chewable tablets

Montelukast Synthon 4 mg is a pink, capsule shaped, biconvex chewable tablet, debossed with “M9UT” and “4” on one side.

Montelukast Synthon 5 mg is a pink, round, biconvex chewable tablet, debossed with “M9UT” and “5” on one side.

The 4 and 5 mg products are dose proportional.

The chewable tablets are packed in Al/Al blister packs.

The excipients are: cellulose, mannitol (E421), croscarmellose sodium, low substituted hydroxypropyl cellulose, cherry flavour, aspartame (E951), iron oxide red (E172), magnesium stearate (E572).

Film-coated tablets

Montelukast Synthon 10 mg is a light-yellow to beige, round, biconvex tablet, debossed with “M9UT” and “10” on one side

The film-coated tablets are packed in Al/Al blister packs.

The excipients are:

Tablet core - cellulose, lactose monohydrate, croscarmellose sodium, low substituted hydroxypropyl cellulose (E463), magnesium stearate.

Coating – hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172).

Pharmaceutical development

The functions of the chosen excipients have been well explained. Also, the packaging is usual and suitable for this type of product. The proposed products have been compared with originator products at different pH values. 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. When compared with the dissolution of the originator both products dissolved more than 85% in 15 minutes. In view of the similar dissolution profiles of the 4 and 5 mg tablets at 3 different pH values, a biowaiver for the 4 mg strength is acceptable from a quality point of view.

Manufacturing process

The manufacturing process for the 4 and 5 mg is a non-standard process in view of the low active substance content (1.73%, i.e. below 2%). As required, the MAH provided additional validation data for 6 batches of the most critical 4 mg strength, demonstrating optimum premixing /blending/lubrication times by variation of these times and determining content uniformity. The process has been successfully validated. For the 10 mg, the manufacturing process is a standard process comprising steps of weighing, two pre-mixings, preparation of the final blend and compression. The process has been described in sufficient detail. The MAH provided validation data on 6 batches.

Control of excipients

Five excipients meet the requirements of the corresponding Ph. Eur. monographs, low substituted hydroxypropyl cellulose and iron oxide red those of the corresponding USP/NF monographs, and cherry flavour is in accordance with Directive EEC 88/388. These specifications are acceptable.

Quality control of drug product

The finished product specification includes tests for appearance, uniformity of mass, hardness, dissolution, identification, assay, uniformity of dosage units, impurities, microbial contamination, identification of excipients. assay, uniformity of dosage units, impurities, microbial contamination, identification of excipients. All analytical methods have been adequately described and the quantitative methods have been sufficiently validated. For various specifications the MAH will tighten or re-evaluate the limits at the end of shelf life, especially for the shelf life lower assay limit, and the shelf life limits for

one impurity and the herewith dependent limit for total impurities. Batch analytical data from 3 batches of each strength have been presented.

Stability of drug product

For all three strengths the claimed shelf life is 2 years without specific storage temperature. All stability results meet the set requirements. For all tablets, there is a minor to slight decrease in assay content as trend, and a corresponding increase in content of one impurity. For the other test parameters there are no clear trends. Herewith the claimed shelf life for is acceptable. Based on the results from photostability studies, the 10 mg tablets are considered to be photostable. Therefore the product does not require any special storage condition. The 4 and 5 mg tablets are however not considered to be photostable and require the storage condition *Store in the original packaging in order to protect the product from light.*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

No excipients are of human or animal origin except for lactose. A BSE/TSE safety statement was provided for lactose, declaring that the milk used for the manufacturing of the excipient is sourced from healthy animals under the same conditions as milk collected for human consumption and the calf rennet used for production of raw material whey is in accordance with the NfG on BSE/TSE. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

These products are generic formulations 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 the first study the pharmacokinetic profile of the test product Montelukast Synthon 5 mg (Synthon B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Singulair junior 5 mg chewable tablets (Dieckmann Arzneimittel GmbH, Germany). In the second study, Montelukast Synthon 10 mg is compared with Singulair 10 mg film-coated tablets (Dieckmann Arzneimittel GmbH, Germany).

The choice of the reference products

The choice of the reference products 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, randomised, laboratory-blind, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy subjects (16 females, 10 males), aged 18-50 years. Each subject received a single dose (5 mg) of one of the 2 montelukast formulations. The tablet was orally administered with 200 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at 0.25, 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 15.0, 18.0, 24.0, and 48.0 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. Twenty-four 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=24	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	1676 ± 452	1709 ± 472	259 ± 51	2.3 (1.0-6.0)	5.8 ± 1.4
Reference	1709 ± 454	1732 ± 468	273 ± 51	2.3 (1.0-4.0)	5.7 ± 0.9
*Ratio (90% CI)	0.99 (0.94-1.04)	0.99 (0.94-1.03)	0.95 (0.92-0.98)	-	-
CV (%)	10	9	6	-	-
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Montelukast Synthron 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.

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.

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.

Bioequivalence study II – 10 mg film-coated tablets

Design

A single-dose, randomised, laboratory-blind, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy subjects (16 females, 10 males), aged 19-48 years. Each subject received a single dose (10 mg) of one of the 2 montelukast formulations. The tablet was orally administered with 200 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected at 0.25, 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 15.0, 18.0, 24.0, and 48.0 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. Twenty-four subjects were included for plasma samples analyses according to the study protocol.

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

Treatment N=24	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	2952 \pm 930	2987 \pm 924	423 \pm 134	3.5 (1.3-6.0)	6.1 \pm 1.9
Reference	2930 \pm 926	2957 \pm 920	414 \pm 133	2.7 (1.3-6.0)	6.5 \pm 1.2
*Ratio (90% CI)	1.01 (0.91-1.12)	1.01 (0.91-1.12)	1.02 (0.89-1.17)	--	--
CV (%)	21	20	22	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Montelukast Synthron 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.

Food effect

If taken in connection with food, montelukast should be taken 1 hour before or 2 hours after food. 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 content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Singulair, approved through Worksharing procedure FI/H/PSUR/0015/001.

Readability test

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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each.

The developed questionnaire contained 17 questions. The questions addressed all the key safety issues and concerns. A sufficient number of questions have been used testing “traceability”, “comprehension” and “applicability”, i.e. can the patient find the information quickly and easily, can he/she understand it and act on it appropriately.

Both rounds showed that, for each question, at least 90% of participants were able to find the correct information, and at least 90% of participants were able to answer the questions correctly. No text revisions were made. However, as 30% of the test participants stated that more highlighting could be used to improve the PL, some more bold was used throughout the leaflet.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Montelukast Synthon 4 mg and 5 mg chewable tablets and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Singulair. 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 consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Montelukast Synthon 4 mg, 5 mg and 10 mg, film-coated tablets were authorised in the Netherlands on 11 November 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states mutually recognised the Dutch evaluation for the marketing authorisation and granted a marketing authorisation. The mutual recognition procedure was finished on 31 May 2011.

A European harmonised birth date has been allocated (25 August 1997) and subsequently the first data lock point for montelukast is July 2012. The first PSUR will cover the period from May 2011 to July 2012, after which the PSUR submission cycle is 3 years.

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

There were no post-approval commitments made during the procedure.

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 _{1/2}	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