CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Montulekast Accord 4 mg and 5 mg chewable tablets
Accord Healthcare B.V., the Netherlands

montulekast (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/1946/001-002/DC
Registration number in the Netherlands: RVG 106626, 106634

25 May 2011

Pharmacotherapeutic group:	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 authorisation in NL:	19 April 2011
Concerned Member States:	Decentralised procedure with AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LV, MT, NO, PL, PT, RO, SE, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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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 Montulekast Accord 4 mg and 5 mg chewable tablets, from Accord Healthcare B.V. The date of authorisation was on 19 April 2011 in the Netherlands.

Montelukast Accord is indicated in children (4mg: aged 2 to 5 years; 5 mg: 6 to 14 years): 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 beta-agonists provide inadequate clinical control of asthma.
Montelukast may also be an alternative treatment option to low-dose inhaled corticosteroids for (4 mg: 2 to 5, 5 mg: 6 to 14) years old 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.
Montelukast is also indicated in the prophylaxis of asthma from (4 mg: 2; 5 mg: 6) years of age and older in which the predominant component is exercise-induced bronchoconstriction.

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 pro-asthmatic 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 beta-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adults and children. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and children 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product SINGULAIR Paediatric 4 mg chewable tablets, registered in Ireland by Merck Sharpe&Dohme Ltd. since 20 February 1998, and SINGULAIR 5 mg purutabletti which have been registered in Finland by Merck Sharpe&Dohme B.V. since 25 August 1997.
In the Netherlands, SINGULAIR 4 mg and 5 mg have been registered since 2001 and 1998 respectively by Merck Sharpe&Dohme (NL license RVG 25800, 23165) 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Singulair 5 mg chewable tablets, registered in the UK. 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. This generic product can be used instead of its reference product.

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, as this is not required for generic medicinal products.

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 this product type 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 montulekast, an established active substance, which is not described in any of the Pharmacopoeia*. The active substance is an off white to yellow coloured hygroscopic powder, which is freely soluble in ethanol (96%), methanol and water, and practically insoluble in acetonitrile. A solubility study of montulekast at different pH and different solvents was provided. There are two possible isomers. The R-isomer is used. The active substance exhibits various polymorphic forms which have been detected by X-Ray Diffraction (XRD). The spectral data indicate that the DMF consistently produces amorphous forms.

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/EMEA 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.

Manufacture
The manufacturing process is described for a certain batch scale size. Adequate specifications are applied for the starting materials, including limitation of the undesired R-enantiomer. The solvents used in the final step have been described.

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. Certificates of analysis of at least three production-scaled batches were submitted with acceptable results.

Stability of drug substance
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed re-test periods of 24 months as well as the storage recommendation, are regarded acceptable and justified by the outcome of the submitted stability studies.

** Pharmacopoeia are official handbooks in which methods of analysis with specifications for substances are laid down by the authorities.*

Medicinal Product

Composition
Montulekast Accord 4 mg – pink colored, mottled, oval, biconvex, chewable tablets, debossed “M4” on one side and plain on other side.
Montulekast Accord 5 mg - pink colored, mottled, round, biconvex chewable tablets, debossed “M5” on one side and plain on other side.

The excipients are - mannitol (E421) (SD 200), microcrystalline cellulose (PH 112), croscarmellose sodium, cherry flavour (501027 AP0551), iron oxide red (E172), aspartame (E951), magnesium stearate.
The tablets are packed into OPA-Al-PVC/Al blisters.
The excipients and packaging are usual for this type of dosage form.
The two formulations are fully dose proportional.

Pharmaceutical development
All tablets: the proposed products have been compared with originator products in several buffer media with Sodium Lauryl Sulphate (SLS). The batches used for the 5 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 bioequivalence studies have been performed with the corresponding German reference products. This test product is acceptable.

Excipients
Except for the cherry flavour and iron oxides where an in house specification is provided, all other excipients comply with their Ph.Eur. monograph. The safety and quality of the cherry flavour has been demonstrated. Magnesium stearate is of vegetable origin.

Container closure system
The Al/Al blister is well known for this type of product. It has been adequately described. The Al-foil consist of the following layers: oPA/adhesive/primer/Al/adhesive/PVC. The foil is in line with Directive 2002/72/EC, Directive 94/62/EG and Ph.Eur. monograph 3.1.11.
The push - thru foil consist of protective lacquer/Al-foil/ heat seal lacquer. The lacquer that comes in contact with the drug product is in line with ResAP (2004)1 and the FDA code of federal regulations CFR21,175.300, “*Resinous and Polymeric Coatings*.” This is considered to be acceptable.
The Al-Al blister is considered to be acceptable as packaging of the drug product.
The LDPE bags have been adequately described and are identified by IR. The declaration from the manufacturer on compliance of LDPE bags with respective EEC/EU regulations has been provided.

Manufacturing process
The drug products are manufactured by direct compression. The sifted materials are blended, granulated and compressed into tablets. The validation has been performed on full-scale batches. The manufacturing process is considered non-standard as the amount of drug substance is less than 2.5% and has been adequately validated for an acceptable production batch size.

Quality control of drug substance
The finished product specification is in general regarded acceptable taking into account all important parameters of the product. The specification limits for related substances are in line with the ICH limits. All the analytical methods have been adequately described and the quantitative methods have been adequately validated. Batch analysis results are provided for two batches of both strengths of the chewable tablets demonstrating compliance with the release specifications.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. Montelukast Paediatric 4 mg and 5 mg chewable tablets fall in the category of BP/Ph.Eur. category 3A products. The microbial testing of solid oral dosage forms is done as per the specification using BP / Ph.Eur. methods. This is acceptable.

Stability tests on the finished product
The stability data of 6 months (accelerated), 12 months (intermediate) and 21 months (long term) demonstrate an increase in resistance to crushing, loss on drying, total impurities but all parameters remain well within the specification at long term and intermediate conditions but are out of specification at accelerated conditions. For the other parameters no clear trends could be observed. Based on the decision tree for data evaluation for re-test period of shelf-life estimation for active substances or finished products the shelf-life that can be granted is 24 months packed in the Al-Al blister with the storage conditions: "*Do not store above 30°C. Store in the original package in order to protect from light and moisture*."
The MAH commits to place the first production batch on long term stability studies throughout the proposed shelf-life, on intermediate stability study condition for 12 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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.2 Non clinical aspects

This product is a generic formulation of SINGULAIR tablets, which are 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 <active substance> 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

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Montulekast Accord 5 mg chewable tablets (Accord Healthcare B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Singulair 5 mg chewable tablets (Merck Sharp & Dohme B.V., UK).

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
An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study was carried out under fasted conditions in 28 healthy male volunteers, aged 18-44 years. One tablet (either test or reference product) containing montelukast sodium 5 mg was placed in the mouth of subjects in the sitting posture after an overnight fast of at least 10 hours. Subjects were instructed to chew the tablet completely (within 2 minutes) and then swallowed with 240 mL of water after proper gargling. The subjects were in sitting posture and the products were administered under sodium vapour lamp covered with red gelatin paper at an ambient temperature. This activity was followed by a mouth check to assess the compliance to dosing. There was a wash-out period of 7 days between study periods.

Subjects remained sitting in upright posture for the first 3 hours after the oral administration. Thereafter, the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. They refrained from drinking water 1 hour before until 2 hours after dosing in each period (except for the water given with the medicine administration).

Blood samples were collected pre-dose and at 0.50, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 20.0, 24.0 and 36.0 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

From the literature it is known that food interacts with the absorption of montelukast. This is clearly stated in the SPC: montelukast should be taken one hour before or two hours after food intake. 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*.

Results
Twenty-six subjects completed both the periods and were included in statistical analysis. Two subjects were withdrawn during the washout period, in which one subject was dosed with reference drug and the other subject was dosed with test drug. One subject was withdrawn on the ground of protocol deviation (positive alcohol screen), whereas another subject was dropped out from the study in Period II due to his own accord.

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

Treatment N = 26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2178 ± 435	2250 ± 443	346 ± 83.4	3.0 (1.5-4.0)	5.1 ± 1.1
Reference	2109 ± 418	2174 ± 442	347 ± 67.7	2.6 (1.75-5.5)	5.0 ± 0.9
***Ratio (90% CI)**	1.03 (0.99-1.08)	1.03 (0.99-1.08)	0.99 (0.91– 1.08)	---	---
CV (%)	9.5	9.4	17.5	---	---

$AUC_{0-\infty}$ 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 montulekast under fasted conditions, it can be concluded that Montulekast Accord 5 mg chewable tablets and the Singulair 5 mg chewable tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
A biowaiver for the 4 mg strength is acceptable, since:
- Montelukast tablets 4 & 5mg are manufactured by the same manufacturing process at

same manufacturing facility.

- Qualitative composition of Montelukast paediatric chewable tablets 4 mg & 5 mg are the same.
- The composition of the strengths are quantitatively proportional i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for both strengths.
- Montelukast exhibits linear pharmacokinetics.
- Dissolution profiles of Montelukast Accord chewable tablets 4 mg are comparable with Montelukast Accord chewable tablets 5 mg.

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).

Risk management plan

Montulekast was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of montulekast can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

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.

A User Test was performed with 20 participants on a leaflet containing both 4 mg and 5 mg strengths. Fourteen questions were asked. The interviewed population covered a range of ages, educational attainments and occupations and both genders were represented. As the products are for use by children aged 2-14 years, the PIL will be read by a parent/guardian. Therefore, it is important to ensure that parents are represented in the interviewed population. No direct questioning was used to ascertain on how many of the participants were parents, however based on the 2001 Census, 48% of the adult population in the England & Wales have children. It was therefore assumed that within the respondents used a percentage would be parents/guardians.

A standard form for recording the results was used, recording the patient's details, scoring or their answers and any comments, as detailed in the report.

No changes to the patient information leaflet were deemed necessary based on the results of the test.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Montulekast Accord 4 mg and 5 mg chewable tablets have a proven chemical-pharmaceutical quality and are a generic form of SINGULAIR Paediatric 4 mg chewable tablets, and SINGULAIR Paediatric 5 mg purutabletti. SINULAIR Paediatric 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, 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Montulekast Accord 4 mg and 5 mg chewable tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 March 2011. Montulekast Accord 4 mg and 5 mg chewable tablets is authorised in the Netherlands on 19 April 2011.

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

The date for the first renewal will be: 31 March 2016.

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

<u>Quality - medicinal product</u>

- The MAH commits to place the first production batch on long term stability studies throughout the proposed shelf-life, on intermediate stability study condition for 12 months.

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