CBG MEB

Public Assessment Report

Scientific discussion

Montelukast Warren 10 mg film-coated tablets

(montelukast sodium)

NL/H/3063/001/DC

Date: 12 November 2015

This module reflects the scientific discussion for the approval of Montelukast Warren 10 mg film-coated tablets. The procedure was finalised on 29 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Montelukast Warren 10 mg film-coated tablets from Warren Generics s.r.o.

The product is indicated in the treatment of asthma as add-on therapy in adolescent of 15 years of age and older and adults with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom “as-needed” short acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom montelukast is indicated in asthma, it can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

Montelukast is indicated in adults and adolescents from the age of 15 years.
A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Singulair 10 mg film-coated tablets (NL License RVG 23164) which has been registered in the Netherlands by Merck Sharp & Dohme B.V. since 1998 through MRP FI/H/0104/001.

The concerned member states (CMS) involved in this procedure were Germany and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Montelukast Warren 10 mg is a beige coloured, rounded square, film coated, biconvex tablets of dimension 8.1 mm x 8.1 mm, plain on both sides.

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

The excipients are:
Tablet core – microcrystalline cellulose (E460), lactose monohydrate, low substituted hydroxylpropyl-cellulose, (E463), croscarmellose sodium (E468), magnesium stearate (E572)
Film coating – hypromellose type 2910 (E464), hydroxypropylcellulose (E463), titanium dioxide (E171), carnauba wax (E903), iron oxide yellow (E172), iron oxide red (E172).

II.2 Drug Substance

The active substance is montelukast sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, hygroscopic powder which is freely soluble in water. A crystalline and an amorphous form are known; the amorphous form is manufactured. The manufacturer consistently produces the R-isomer with trans configuration. The S-isomer is controlled as an impurity.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur., supplemented by the MAH with in-house methods for residual solvents, polymorphic form, sodium content and particle size distribution.
The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial size batches of drug substance. Additionally, certificates of analysis have been provided for the active substance batch used in three batches of finished product.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients are well known. The choices for the packaging and manufacturing process (direct compression) are justified. The composition of the batch used in the bioequivalence study is identical to the final formulation chosen.
To assess the similarity of Montelukast Warren 10 mg and Singulair 10 mg tablets in terms of dissolution characteristics, dissolution profiles were obtained for the test biobatch and the reference biobatch, respectively, in media with pH 1.2, 4.5, 6.8 (all with 0.5% sodium lauryl sulfate) and in water with 0.5% sodium lauryl sulfate (testing medium for batch release). The use of a surfactant was sufficiently justified. The results show that equivalence between test and reference product was demonstrated *in vitro* in dissolution media with the requested pH values.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
A flow chart and a description of the manufacturing process have been provided, including in-process controls. The tablets are manufactured by sifting, dry mixing and lubrication, followed by compression of lubricated granules, preparation of coating solution and film coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot-scale batches.
The product is manufactured using conventional manufacturing techniques. Process validation for three full-scale batches will be performed post authorisation.

Control of excipients
All ingredients are tested according to the Ph.Eur. monographs, with the exception of low substituted hydroxypropylcellulose (complying with USP-NF monograph). The coating material including the iron oxides (Colorcon®), are non-compendial excipient mixtures. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, uniformity of dosage units, water, average weight, tablet thickness, dissolution, assay, related substances and microbiological examination. The release and shelf-life limits are not identical.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three pilot scale batches stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in blister packs (OPA-Alu-PVC/Alu).
At all conditions increases were observed in one impurity. Total impurities during intermediate and long-term studies were increased. Significant changes occurred at the accelerated condition. All other

parameters examined remain relatively stable throughout the test periods and at all three test conditions and within specification.
A shelf life of 30 months can be assigned based on the 24 month long term data. Based on the results of a photostability study and given the fact that the water content of the tablets is relatively high, the product should be stored in the original package in order to protect from moisture and light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is derived from material of vegetable origin. TSE free certification has been provided with regard to the lactose monohydrate being used.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Montelukast Warren has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to perform process validation on three commercial-scale batches.
- The MAH committed to continue the ongoing long-term stability studies as per stability protocol (48 months).

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Montelukast Warren 10 mg 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Montelukast 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Montelukast Warren 10 mg (Warren Generics s.r.o., Czech Republic) is compared with the

pharmacokinetic profile of the reference product Singulair 10 mg film-coated tablets (Merck Sharp & Dohme BV, the Netherlands).

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.

Bioequivalence studies

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male and female subjects, aged 21-42 years. Each subject received a single dose (10 mg) of one of the 2 montelukast formulations. The tablet was orally administered with 240 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 pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours after administration of the products.

As the t_{max} of orally administered montelukast is about 2- 3 hours and the elimination half life about 5 hours, the sampling scheme is agreed upon. No positive predose concentrations were found demonstrating that a 7-day washout period is long enough. Montelukast film-coated tablets can be taken irrespectively with mealtimes, therefore demonstration of bioequivalence under fasting conditions is in agreement with the NfG CPMP/EWP/QWP/1401/98/Rev1 on the investigation of bioequivalence. Overall the study design is adequate for the purpose of this study.

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
Four subject were dropped out as they did not report to study center for period II. A total of 24 subjects completed the clinical phase of the study successfully. The plasma samples of these 24 subjects were analyzed and considered for statistical analysis.

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	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3475 ± 1263	3610 ± 1339	537 ± 216	3.33 (1.00 – 6.00)	--
Reference	3372 ± 1094	3509 ± 1199	535 ± 182	2.66 (1.50 – 5.50)	--
***Ratio (90% CI)**	1.00 (0.88 – 1.13)	1.00 (0.88 – 1.13)	0.96 (0.83 – 1.10)	--	--
CV (%)	26	26	29	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**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 Montelukast Warren 10 mg is considered bioequivalent with Singulair 10 mg film-coated tablets.

A total of two adverse events (headache and vomiting) were reported during the clinical phase of the study. The adverse events were mild in severity and were resolved by the end of the study. No serious adverse events were observed during both the study periods.

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).

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 Montelukast Warren.

- Summary table of safety concerns as approved in RMP

Important identified risks	--
Important potential risks	Depression in paediatric patients Suicidality in paediatric patients
Missing information	--

The member states 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. 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 (PL) 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 results show that the percentage of participants successfully finding the section and answering the questions correctly was within the acceptable percentage outlined in the protocol and was 90% or more. 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. No changes were made to the PL during the user testing process.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Montelukast Warren 10 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Singulair 10 mg. 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.

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 Montelukast Warren 10 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 January 2015.

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