COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Montelukast Amarox 10 mg, film-coated tablets

(montelukast)

NL/H/4943/001/DC

Date: 5 January 2021

This module reflects the scientific discussion for the approval of Montelukast Amarox 10 mg, film-coated tablets. The procedure was finalised at 15 October 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Montelukast Amarox 10 mg, film-coated tablets, from Amarox Pharma B.V.

The product is indicated 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 β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom the product is indicated in asthma, Montelukast Amarox can also provide symptomatic relief of seasonal allergic rhinitis.

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

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 which has been registered in Finland by Merck Sharp & Dohme B.V. since 1997. In the Netherlands, Singulair 10 mg film-coated tablets (NL License RVG 23164) has been registered since 3 November 1998 by the procedure FI/H/0104/001/MR.

The concerned member states (CMS) involved in this procedure were Spain and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Montelukast Amarox is a beige, rounded square-shaped film-coated tablet. Each film-coated tablet contains montelukast sodium, which is equivalent to 10 mg montelukast.

The film-coated tablets are packed in Alu-Alu Blisters.

The excipients are:
Tablet core - lactose monohydrate, mannitol (E421), croscarmellose sodium, hydroxypropyl cellulose (E463), cellulose microcrystalline (PH112) and magnesium stearate
Film coating - hypromellose 6cP (E464), titanium dioxide (E171), hydroxy propyl cellulose (E463), carnauba wax, iron oxide yellow (E172) and 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 drug substance is a white or almost white hygroscopic powder and is freely soluble in water, but very slightly soluble in 0.1N hydrochloric acid and practically insoluble in buffers pH 4.5 and 6.8. The active substance shows polymorphism and is manufactured having the same amorphous form as that of the reference product. The active substance is a chiral compound with one chiral centre.

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 Ph.Eur.

Manufacturing process

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

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP with additional tests for residual solvents, identity, particle size distribution and microbial examination. Batch analytical data demonstrating compliance with this specification have been provided for five production scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 2 years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the reference product. The main development studies described in the dossier were the characterisation of the reference products, formulation optimisation studies, dissolution method development and the performance of comparative dissolution studies at three pH's. The drug product batch used in the bioequivalence study

was manufactured according to the finalised composition and manufacturing process and is representative. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are the dry mixing, wet granulation, drying, blending and lubrication and compression. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for six pilot scaled batches and three full-scaled batches in accordance with the relevant European guidelines. The product is manufactured using standard manufacturing techniques.

Control of excipients

Except for cellulose microcrystalline, the excipients comply with Ph.Eur. requirements, including control of relevant functionality-related characteristics. For cellulose microcrystalline the identification test has been included in the specification. The specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, water content, uniformity of dosage units, dissolution, related substances, assay, microbiological quality and identification of colourants. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six pilot scaled batches and one full scaled batch from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches stored at 25°C/60% RH (36 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 Alu-Alu blister. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are: 'This medicinal product does not require any special temperature storage conditions. Store in the original blister in order to protect from moisture'.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Montelukast Amarox has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Montelukast Amarox 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 Amarox 10 mg, film-coated tablets (Amarox Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Singulair 10 mg film-coated tablets (Merck Sharp & Dohme B.V., NL).

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

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 18-39 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 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.33, 5.67, 6, 7, 8, 10, 12, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable. A single dose study using 10 mg tablet is adequate to support the application for the proposed immediate-release product. The conduct of the study under fasting conditions is appropriate as the proposed product can be taken with or without food.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject was withdrawn due to protocol non-compliance and one subject did not report to the facility. Hence, 36 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=36	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	3094 ± 1166	3186 ± 1192	487 ± 242	4.91 (3.09– 6.83)
Reference	2984 ± 1051	3078 ± 1061	464 ± 201	4.87 (3.13– 7.61)
***Ratio (90% CI)**	1.02 (0.91–1.14)	1.01 (0.91–1.13)	1.02 (0.88 – 1.19)	--

$AUC_{0-\infty}$	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

**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 Amarox is considered bioequivalent with Singulair.

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 Amarox.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Montelukast 10 mg film-

coated tablets (content) and Levetiracetam Hetero 750 mg film-coated tablets (layout). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Montelukast Amarox 10 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of 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 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 Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 October 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse