COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Montelukast AMETAS 4 mg and 5 mg chewable tablets
Montelukast AMETAS 10 mg film-coated tablets

(montelukast sodium)

NL/H/4858/001-003/DC

Date: 24 July 2020

This module reflects the scientific discussion for the approval of Montelukast AMETAS. The procedure was finalised on 29 April 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 AMETAS 4 mg and 5 mg chewable tablets, and 10 mg film-coated tablets from AMETAS medical GmbH.

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 SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Singulair 4 mg and 5 mg chewable tablets and Singulair 10 mg film-coated 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 RVG 23164-23165) has been registered since 1998 by the procedure FI/H/0104/001-002/MR, and the authorisation for Singulair 4 mg was recognised through MRP in 2001 (FI/H/0104/003).

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Montelukast AMETAS 4 mg is a pink, flat, round tablet with beveled edges, marked with '4' on one side and plain on the other. One chewable tablet contains montelukast sodium, which is equivalent to 4 mg montelukast.
Montelukast AMETAS 5 mg is a pink, flat, round, chewable tablet with beveled edges. One chewable tablet contains montelukast sodium, which is equivalent to 5 mg montelukast.
Montelukast AMETAS 10 mg is a beige, round, biconvex film-coated tablet. One film-coated tablet contains montelukast sodium, which is equivalent to 10 mg montelukast.

The tablets are packed in Aluminium/Aluminium blister packs.

The excipients are:
4 and 5 mg chewable tablets
mannitol spray dried (E 421), microcrystalline cellulose (E 460), aspartame (E 951), low-substituted hydroxypropyl cellulose, iron oxide red (E 172), croscarmellose sodium, cherry flavour, magnesium stearate

The 4 mg and 5 mg chewable tablet strengths are fully dose proportional.

10 mg film-coated tablets
Tablet core - mannitol spray dried (E 421), microcrystalline cellulose (E 460), low-substituted hydroxypropyl cellulose, croscarmellose sodium, banana flavor, aspartame (E 951), magnesium stearate
Coating - hypromellose 3cP, hydroxypropylcellulose, talc, titanium dioxide, iron oxide yellow (E 172), iron oxide red (E 172)

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, which is freely soluble in water and in methylene chloride, and freely soluble to very soluble in ethanol. The active substance contains one chiral centre and is the R-isomer. A crystalline and an amorphous form are known. The amorphous form is used.

The CEP procedure is used for both manufacturers of 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
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The MAH presented a set of specifications, including the additional requirements from both CEPs for residual solvents and particle size. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches from one CEP holder and three batches from the second CEP holder.

Stability of drug substance
For the first manufacturer, 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.
The re-test period of the drug substance from the other manufacturer is 36 months when stored under the stated conditions. This claim is supported by 36 months long term and 6 months accelerated stability data.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were formulation studies. The excipients are well known and the choices of the packaging and manufacturing process have been justified. All strengths of the proposed products have been compared with originator products in buffer media of pH 1.2-4.5-6.8 and in water with 0.5% SLS. Dissolution profiles are similar between the originator and the proposed products.
Bioequivalence studies were performed with the 5 mg and 10 mg drug product versus the Greek reference product. The batches used in the bioequivalence studies have the same composition and are manufactured in the same way as the future commercial batches. The biowaiver for the 4 mg strength is acceptable from a chemical-pharmaceutical point of view. The proposed particle size specification for the drug substance is adequately justified in view of the biobatch and the dissolution profiles. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process of the 4 mg and 5 mg chewable tablets is divided in the following steps: pre-mixing-mixing, sizing-sieving, mixing, lubrication, compression and packaging. The manufacturing process of the 10 mg film-coated tablets is divided in the following steps: pre-mixing-mixing, sizing-sieving, mixing, lubrication, compression, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production

scale batches of each strength of chewable tablets and one pilot-scale and two production scale batches of the film-coated tablets. The product is manufactured using conventional manufacturing techniques. Process validation for further full-scale batches will be performed post authorisation.

Control of excipients

All ingredients are tested following the Ph.Eur. monographs, with the exception of flavours, low-substituted hydroxypropyl cellulose, coating agent and Iron oxide red.
Flavours (cherry and banana) and coating agent comply with an in house specification, low-substituted hydroxypropyl cellulose complies with the USP-NF, and Iron oxide red complies with Commission Regulation (EU)231/2012. The specifications are acceptable.

Quality control of drug product

The product specification of the chewable tablets includes tests for appearance, identification, water content, average weight, dimensions, dissolution, uniformity of dosage units, assay, related substances, identification of colorant and microbiological purity. The release and shelf life limits are identical except for water content.
The product specification of the film-coated tablets includes tests for appearance, identification, water content, average weight, disintegration time, dimensions, dissolution, uniformity of dosage units, assay, related substances, identification of colorants and microbiological purity. The release and shelf life limits are identical except for water content.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production sites have been provided on three production-scale batches of each strength of chewable tablets and one pilot-scale and two production scale batches of the film-coated tablets, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three production-scale batches of each strength of the chewable tablets and one pilot-scale and two production scale batches of the film-coated tablets, 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 Al/Al blisters.
Increases in related substances were observed in all drug products at both conditions. The increases were more pronounced in the chewable tablets and accelerated conditions. All results for related substances remained within specification limits. All other parameters tested remain relatively stable in both tablets strengths and at both storage conditions. The tablets should be stored in the original packaging to protect from light, as out of specification results were demonstrated in photostability testing. Based on the stability data provided the proposed shelf life of 24 months was granted.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is derived from material of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Montelukast AMETAS 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 AMETAS 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Montelukast AMETAS 5 mg and Montelukast AMETAS 10 mg (AMETAS medical GmbH, Germany) is compared with the pharmacokinetic profile of the reference products Singulair 5 mg chewable tablets and Singulair 10 mg film-coated tablets (Merck, Sharp & Dohme Ltd, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence studies 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.

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.

Biowaiver
A waiver for the montelukast 4 mg chewable tablets was granted as all of the following conditions are fulfilled:

- the drug input for chewable tablets is linear from 2 to 10 mg
- both strengths are manufactured by the same manufacturing process
- the qualitative composition of the two strengths is the same
- the composition of the two strengths is quantitatively proportional
- appropriate in vitro dissolution data were provided.

The results of the bioequivalence study performed with the 5 mg strength therefore apply to the 4 mg strength as well.

Bioequivalence studies

Bioequivalence study I – 5 mg chewable tablets
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 58 healthy subjects (50 males/8 females), aged 29.60 ± 6.55 years. Each subject received a single dose (5 mg) of one of the 2 montelukast formulations after an overnight fast of at least 10 hours. Each subject was asked to slowly and thoroughly chew the tablet. A mouth check was performed immediately after the subject indicated that the tablet was completely chewed. Once this was confirmed the subject was asked to swallow the chewed tablet mass. Drinking water

was not allowed between 2 hours pre-dose and 2 hours post-dose. At all other times water was given ad-libitum. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.50, 1, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 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 pre-dose concentrations were found demonstrating that a 7-day washout period is long enough.
Overall the study design is adequate for the purpose of this study. The montelukast 5 mg tablets are chewable tablets and the tablets were administered without intake of water. This is the most sensitive situation to demonstrate bioequivalence of chewable tablets.

Results
One subject was withdrawn from the study on the enrolment day of period II due to a positive urine drug abuse test result. Another subject dropped out from the study during period II at 21:30 hours at his personal request. The results of this subject were included in the statistical analysis although the last time point was not sampled in the second period. Pharmacokinetic analysis was performed on data from 57 subjects.

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

Treatment N=57	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1430 ± 438	1505 ± 449	261 ± 63	2.25 (1.0-5.0)	4.2 ± 1.3
Reference	1520 ± 426	1600 ± 432	284 ± 61	2.5 (1.0-5.0)	4.3 ± 1.2
***Ratio (90% CI)**	0.94 (0.90 – 0.97)	0.94 (0.90 -0.97)	0.92 (0.88 – 0.96)	--	--
CV (%)	12	11	15	--	--

$AUC_{0-\infty}$ 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 within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Montelukast AMETAS 5 mg is considered bioequivalent with Singulair 5 mg.

Bioequivalence study II – 10 mg film-coated tablets

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 58 healthy subjects (52 males/6 females), aged 29.69 ± 6.76 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. Drinking water was not allowed between 1 hour pre-dose and 2 hours post-dose. At all other times water was given ad-libitum. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 5, 6, 7, 8, 10, 12 and 24 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 pre-dose concentrations were found demonstrating that a 7-day washout period is long enough. 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

One subject was withdrawn from the study in period-II due to adverse event (vomiting). Another subject dropped out from the study for personal reasons. Pharmacokinetic analysis was performed on data from 56 subjects.

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

Treatment N=56	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2443 ± 729	2531 ± 763	396 ± 121	3.5 (1.0-6.0)	4.9 ± 1.0
Reference	2659 ± 905	2755 ± 961	443 ± 153	3.0 (1.0-6.0)	4.9 ± 1.0
***Ratio (90% CI)**	0.93 (0.87 - 0.99)	0.93 (0.87 – 0.99)	0.90 (0.83 – 0.98)	--	--
CV (%)	22	21	28	--	--

$AUC_{0-\infty}$	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 within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Montelukast AMETAS 10 mg is considered bioequivalent with Singulair 10 mg.
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).

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 AMETAS.

Table 3. 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 bioequivalence studies 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 full user testing report has been provided for the package leaflet (PL) of Montelukast AMETAS 10 mg film-coated tablets. A bridging report & focus test is provided for Montelukast AMETAS 4 and 5 mg chewable tablets (focus test for aspects of the montelukast 4 and 5 mg chewable tablets PL which are not addressed in the montelukast 10

mg film-coated tablets PL). The textual and visual differences between the tested and proposed PLs have been outlined and analysed in supplementing reports. The member states agree that the PLs for the chewable tablets require no separate user testing due to their similarity to the already tested PLs.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Montelukast AMETAS 4 mg and 5 mg, chewable tablets and Montelukast AMETAS 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 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 AMETAS with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 April 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