COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Maraviroc Amarox 150 mg and 300 mg film-coated tablets (maraviroc)

NL/H/5615/001-002/DC

Date: 2 January 2025

This module reflects the scientific discussion for the approval of Maraviroc Amarox 150 mg and 300 mg film-coated tablets. The procedure was finalised on 15 February 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Maraviroc Amarox 150 mg and 300 mg film-coated tablets, from Amarox Pharma B.V.

The product is, in combination with other antiretroviral medicinal products, indicated for: treatment-experienced adults, adolescents and children of 2 years of age, and older and weighing at least 10 kg infected with only CCR5-tropic HIV-1 detectable.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Celsentri 150 mg and 300 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/07/418) since 18 September 2007.

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

II. QUALITY ASPECTS

II.1 Introduction

Maraviroc Amarox 150 mg and 300 mg are film-coated tablets. The two strengths of the film-coated tablets can be distinguished by the size and debossing and are as follows:

Maraviroc Amarox 150 mg
The 150 mg strength tablets are blue, oval, biconvex, film-coated, approximate dimensions 8.7 mm x 15.7 mm and debossed with “HM” on one side and “150” on the other side. Each film-coated tablet contains as active substance 150 mg maraviroc.

Maraviroc Amarox 300 mg
The 300 mg strength tablets are blue, oval, biconvex, film-coated, approximate dimensions 19.4 mm x 10.7 mm and debossed with “HM” on one side and “300” on the other side. Each film-coated tablet contains 300 mg maraviroc.

The excipients are:
Tablet core - microcrystalline cellulose (E460), sodium starch glycolate (Type A), silica, colloidal anhydrous, magnesium stearate (E470b) and calcium hydrogen phosphate (E341).
Film-coat - poly (vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171), macrogol (MW3350) (E1521), lecithin (soya) (E322) and indigo carmine aluminium lake (E132).

The two tablet strengths are dose proportional.

The film-coated tablets are either packed in aluminium-polyvinyl chloride/polychlorotrifluoroethylene (Alu-PVC/Aclar) blisters or high density polyethylene (HDPE) containers with child-resistant closure.

II.2 Drug Substance

The active substance is maraviroc, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is insoluble in water. For this product, polymorphic form B is consistently produced. The active substance has one chiral centre.

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 first intermediate is manufactured from a starting material in three chemical transformation steps with one isolated intermediate. The second intermediate is manufactured from a starting material in two chemical transformation steps with one isolated intermediate. The active substance is manufactured from the two intermediates in three chemical transformation steps with three isolated intermediates. The third starting material is introduced in the third stage and is manufactured in a one-step synthesis. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 3 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 Celsentri and the pharmaceutical development of the product has been adequately performed. The comparative dissolution complementary to the bioequivalence study are acceptable and according to the requirements of the EMA guideline on investigation of bioequivalence. The comparative dissolution data in support of biowaiver of strength are acceptable. The dissolution method is acceptable and sufficient discriminatory power is demonstrated.

Manufacturing process

The film-coated tablets are manufactured by dry granulation. The manufacturing process has been validated according to relevant European/ICH guidelines.

Control of excipients

The choice of excipients is justified and their functions explained. The excipients comply with Ph.Eur. monographs or in-house requirements. These 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 appearance, identification, average mass of tablets, water content, content uniformity, related compounds, assay, microbial examination and identification of the colorant. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three submission batches of each strength 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 batches of each strength stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). Furthermore, stability results for only the dissolution parameter are included for 33 months at long term conditions and it is shown that all results comply to the dissolution limit. The stability was tested in accordance with applicable European guidelines. Photostability studies showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years. No specific storage conditions needed to be included in the SmPC or on the label.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Maraviroc 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 Maraviroc Amarox is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Celsentri which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Maraviroc is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Maraviroc Amarox 300 mg film-coated tablets (Amarox Pharma B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Celsentri 300 mg film-coated tablets (ViiV healthcare B.V., the Netherlands). In addition, the MAH requested a biowaiver for the lower 150 mg strength.

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

Biowaiver

A biowaiver for the 150 mg strength is granted according to the EMA Bioequivalence guideline, based on the following criteria:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. 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 all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f2 similarity factor values were within criteria (>50%). An f2 value between 50 and 100% suggests that the two dissolution profiles are similar.
Based on the manufacturing procedure, tablet composition and comparative dissolution data a biowaiver can be granted for the additional strength 150 mg film-coated tablets, referring to the demonstrated bioequivalence for the 300 mg strength with the reference product.

Bioequivalence study C1B02098

Design

A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 20-44 years. Each subject received a single dose (300 mg) of one of the two maraviroc formulations. The tablet was orally administered with 240 mL water after an overnight fasting period of at least 8 hours. There were two dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable.

Maraviroc may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of maraviroc. 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.

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
There were 56 subjects enrolled in the study, one subject was withdrawn after period 1, because of a positive drugs of abuse scan during period 2 check-in. 55 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of maraviroc, 300 mg under fasted conditions.

Treatment N=55	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3061 ± 928	3190 ± 960	909 ± 327	3.00 (0.67 – 5.50)
Reference	3115 ± 919	3240 ± 949	880 ± 272	3.37 (1.33 – 6.00)
***Ratio (90% CI)**	0.98 (0.93 – 1.03)	-	1.02 (0.95 – 1.10)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 36 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Maraviroc Amarox 300 mg is considered bioequivalent with Celsentri 300 mg. The results of study C1B02098 with the 300 mg formulation can be extrapolated to the other strength 150 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6. A biowaiver for the 150 mg strength can therefore be granted.

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 Maraviroc Amarox.

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

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant women

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 Celsentri. 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 content is in line with that of the innovator product Celsentri 150 mg and 300 mg film-coated tablets.
A user consultation with target patient groups on the design and layout of the package leaflet (PL) has been performed on the basis of a bridging report making reference to Levetiracetam Hetero 750 mg film-coated tablets, PT/H/515/01-04/DC. 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

Maraviroc Amarox 150 mg and 300 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Celsentri 150 mg and 300 mg film-coated tablets. Celsentri 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 Maraviroc Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 February 2024.

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
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.