COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5813/001-002/DC

Date: 27 May 2025

This module reflects the scientific discussion for the approval of Maraviroc Waymade 150 mg and 300 mg film-coated tablets. The procedure was finalised on 24 May 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 Waymade 150 mg and 300 mg film-coated tablets, from Waymade 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 Austria, France, Germany, Italy, Portugal and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Maraviroc Waymade 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 Waymade 150 mg
The 150 mg film-coated tablets are white to off white, biconvex oval shaped, debossed with "NAV" and "125" one side and plain on other side with approximate dimensions 8.7 mm x 15.8 mm. Each 150 mg film-coated tablet contains as active substance 150 mg maraviroc.

Maraviroc Waymade 300 mg
The 300 mg film-coated tablets are white to off white, biconvex oval shaped, debossed with "NAV" and "124" one side and plain on other side with approximate dimensions 10.7 mm x 19.2 mm. Each 300 mg film-coated tablet contains as active substance 300 mg maraviroc.

The excipients are:
Tablet core - microcrystalline cellulose (E460), calcium hydrogen phosphate anhydrous (E341), sodium starch glycolate (Type A), hypromellose Type 2910 (E464) and magnesium stearate (E470b).
Film-coat - poly(vinyl alcohol) partially hydrolysed (E1203), titanium dioxide (E171), macrogols (E1521) and talc (E553b).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in polyvinyl chloride-polyvinylidene chloride/aluminium (PVC-PVDC/Alu) blisters in a carton.

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 white to off-white crystalline powder and is insoluble in water. The active substance exhibits polymorphism and polymorphic form B is consistently produced.

Manufacturing process
The manufacturing process starts from three starting materials in a four step process. Adequate specifications have been adopted for starting materials, solvents and reagents. The control of genotoxic impurities is in line with ICH M7. 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 ICH Q2A. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 12 months. Based on the data submitted, a retest period could be granted of 36 months 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 in principle justified and their function explained, and critical quality attributes have been defined. The *in vitro* dissolution studies complementary to the bioequivalence studies and the biowaiver of strengths have been adequately conducted. Suitability for the pediatric population has been adequately discussed.

Manufacturing process
The manufacturing process consists of the following steps: dispensing, sifting binder solution preparation, pre-mixing, granulation, drying of granules, sifting and milling, extra granular sifting, (pre)lubrication, compression, preparation of coating dispersion, coating, drying, and packaging. Information on the critical process parameters has been provided. The manufacturing process has been validated according to relevant European/ICH guidelines.

Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with their Ph.Eur and in-house requirements and functionality related characteristics are tested where relevant. 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 description, identification (by UV and HPLC), water content, uniformity of dosage units by weight variation, dissolution, disintegration time, 4,4-difluorocyclohexane carboxylic acid, related substances, assay, microbial enumeration and specified microorganisms. 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 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 from three batches of each strength stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability study in accordance with ICH Q1B was investigated and the product was found to be photostable. On basis of the data submitted, a shelf life was granted of 30 months. 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 Waymade 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 Waymade 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 one 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 Waymade 300 mg film-coated tablets (Waymade B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Celsentri 300 mg film-coated tablets (ViiV Healthcare UK Ltd, United Kingdom).

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 lower (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 comparative dissolution profiles were tested in three media (1.2 pH, 4.5 pH and 6.8 pH). The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. With a f2 value of 58, similar dissolution profiles between the 300 mg and 150 mg strength can be concluded.
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 studies

Design

A double blinded, single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 18-42 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 a fasting period of 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 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
3 subjects were withdrawn from the study due to personal reasons. 51 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=51	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3993 ± 1127	4104 ± 1134	1082 ± 366	3.00 (0.75 – 5.00)
Reference	3879 ± 1236	3992 ± 1244	1029 ± 385	3.00 (0.50 – 5.03)
***Ratio (90% CI)**	1.04 (0.97 – 1.10)	-	1.05 (0.96 – 1.14)	-

$AUC_{0-\infty}$	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 = 72 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Maraviroc Waymade 300 mg is considered bioequivalent with Celsentri 300 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).

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 Waymade.

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

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 Celsentri 150 mg and 300 mg film-coated tablets, EMEA/H/C/000811 for key safety messages and content and to Doxycycline 50 mg and 100 mg capsules, PL 06464/3107 for design and 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

Maraviroc Waymade 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 Waymade with the reference product, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 24 May 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
NL/H/5813/1-2/IA/001	Change to importer, batch release arrangements and quality control testing of the finished product - Addition of a manufacturer responsible for importation and/or batch release – Not including batch control/testing	Yes	4 November 2024	Approved	N.A.
NL/H/5813/1-2/IA/002	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Minor changes to an approved test procedure	No	15 January 2025	Approved	N.A.