



Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Maraviroc 150 mg film-coated tablets

Maraviroc 300 mg film-coated tablets

Maraviroc

PL 49445/0307-0308

Amarox Limited

LAY SUMMARY

Maraviroc 150 mg film-coated tablets Maraviroc 300 mg film-coated tablets

Maraviroc

This is a summary of the Public Assessment Report (PAR) for Maraviroc 150 mg and 300 mg film-coated tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Maraviroc film-coated tablets in this lay summary for ease of reading.

For practical information about using Maraviroc film-coated tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Maraviroc film-coated tablets and what are they used for?

Maraviroc film-coated tablets are a generic medicine. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Celsentri 150 mg and 300 mg film-coated tablets.

Maraviroc is used to treat Human Immunodeficiency Virus type-1 (HIV-1) in adults and adolescents weighing at least 30 kg.

Maraviroc must be taken in combination with other medicines which are also used to treat the HIV infection. These medicines are all called anti-HIV medicines or antiretrovirals.

How do Maraviroc film-coated tablets work?

Maraviroc film-coated tablets contain a medicine called maraviroc. Maraviroc belongs to a group of medicines called CCR5 antagonists. Maraviroc works by blocking a receptor called CCR5 which HIV uses to enter and infect blood cells.

Maraviroc, as part of combination therapy, reduces the amount of virus in the body, and keeps it at a low level. This helps the body to increase the CD4 cell count in the blood. CD4 cells are a type of white blood cell that are important in helping the body to fight infection.

How are Maraviroc film-coated tablets used?

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral.

The recommended dose of maraviroc tablet in adults is 150 mg, 300 mg or 600 mg twice per day depending on other medicines that the patient is taking at the same time. Patients should always take the dose recommended by their doctor.

If the patient has a kidney problem, their doctor may alter their dose. The patient should talk to their doctor if this applies to them.

Maraviroc film-coated tablets can be taken with or without food.

For further information on how Maraviroc film-coated tablets used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

The medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Maraviroc film-coated tablets have been shown in studies?

Because Maraviroc film-coated tablets are a generic medicine, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Maraviroc film-coated tablets?

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Maraviroc film-coated tablets are a generic medicine, and/or are bioequivalent to the reference medicines, their benefits and possible side effects are taken as being the same as the reference medicine.

Why were Maraviroc film-coated tablets approved?

It was concluded that, Maraviroc film-coated tablets have been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Maraviroc film-coated tablets?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Maraviroc film-coated tablets. The RMP details the important risks of Maraviroc film-coated tablets, how these risks can be minimised, any uncertainties about Maraviroc film-coated tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Maraviroc film-coated tablets:
Important identified risks:

- Hepatotoxicity
- Postural hypotension

Important potential risks:

- Potential to alter immune function:
 - Infections

- Malignancies
- Autoimmune Disease
- Delayed-type hypersensitivity reactions
- Ischaemic cardiac disorders
- Muscular toxicity (rhabdomyolysis, myositis), change in the observed HIV tropism
- Drug resistance – HIV mutations impacting CCR5 interactions
- Potential for QT prolongation
- Potential for medication error (dosing) in children due to drug-drug interactions

Missing information:

- Use in pregnant or lactating women
- Long term safety in children and adolescents

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Maraviroc film-coated tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Maraviroc film-coated tablets

A Marketing Authorisation for Maraviroc film-coated tablets was granted in the United Kingdom (UK) on 24 July 2024.

The full PAR for Maraviroc film-coated tablets follows this summary.

This summary was last updated in September 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Maraviroc 150 mg and 300 mg film-coated tablets (PL 49445/0307-0308), could be approved.

The products are approved for the following indication:

In combination with other antiretroviral medicinal products, for treatment-experienced adults and adolescents weighing at least 30 kg infected with only CCR5-tropic HIV-1 detectable (see SmPC sections 4.2 and 5.1).

The active substance is maraviroc.

Maraviroc is a member of a therapeutic class called CCR5 antagonists. Maraviroc selectively binds to the human chemokine receptor CCR5, preventing CCR5-tropic HIV-1 from entering cells.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicines of a suitable originator medicinal products, Celsentri 150 mg and, 300 mg film-coated tablets, that have been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 26 October 2023, due to issues relating to quality, safety and efficacy. Further data was presented to the CHM on 30 May 2024. On the further evidence before it, the CHM advised the grant of Marketing Authorisations.

Marketing Authorisations for Maraviroc 150 mg and 300 mg film-coated tablets were granted in the United Kingdom (UK) on 24 July 2024.

II QUALITY ASPECTS

II.1 Introduction

Each Maraviroc 150 mg film-coated tablet contains 150 mg of maraviroc.

Each Maraviroc 300 mg film-coated tablet contains 300 mg of maraviroc.

In addition to maraviroc these products also contains the following excipients:

Core:

Cellulose, microcrystalline,
sodium starch glycolate (type A), silica, colloidal anhydrous, magnesium stearate and
calcium hydrogen phosphate.

Film coating:

Poly (vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171), macrogol (MW3350)
(E1521), lecithin (soya) (E322) and indigo carmine aluminium lake (E132)

The finished products are packaged in clear PVC/Aclar-aluminium blister packs containing
60 film-coated tablets or a high density polyethylene bottle, with child resistant plastic cap,
with a pulp liner, containing 60 tablets..

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging
components. All primary packaging complies with the current regulations concerning
materials in contact with food.

II.2 ACTIVE SUBSTANCE

r INN:

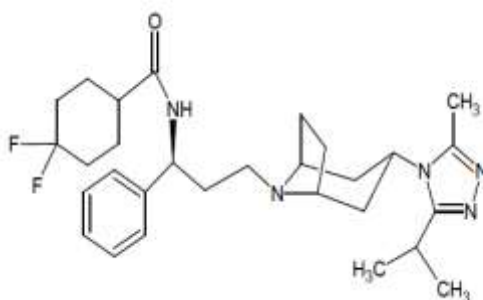
Maraviroc

Chemical names:

i. 4,4-Difluoro-N-[(1S)-3-[(3-exo)-3-[3-methyl-5-(1-methylethyl)-4H-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-cyclohexanecarboxamide

ii. N-[(1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-4,4-difluorocyclohexanecarboxamide

Chemical Structure:



Molecular Formula:

C₂₉H₄₁F₂N₅O

Molecular weight:

513.67

Appearance:

A white to an off-white powder

Solubility:

Soluble in Ethanol

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS**III.1 Introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of maraviroc are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of maraviroc is well-known. With the exception of data from a single bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study.

Bioequivalence study-C1B02098

This was a, randomised, two-period, two-treatment, two-sequence, crossover, balanced, single dose, oral bioequivalence study comparing the test product Maraviroc 300 mg film-coated tablets versus the reference product) Celsentri 300 mg film-coated tablets (maraviroc), in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least 8 hours, a single 300 mg oral dose of investigational product was administered to the subjects in a sitting posture with about 240 mL of water at ambient temperature, under the supervision of trained study personnel in each study period.

Blood samples were taken pre-dose and up to 36 hours post dose, with a washout period of 5 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1. Descriptive statistics

Pharmacokinetic Parameter	Arithmetic Means ($\pm$ SD)	
	Test Product-T	Reference Product-R
AUC (ng/mL)*(hr)	3061.451($\pm$ 927.831)	3114.598 $\pm$ 919.068
AUC _i (ng/mL)* (hr)	3189.813($\pm$ 959.773)	3240.285 $\pm$ 948.952
C _{max} (ng/mL)	908.59($\pm$ 327.072)	880.358 ($\pm$ 271.681)
T _{max} ¹ (hr)	3.000(0.667-5.500)	3.366 (1.333-6.000)

¹ Median (Min, Max)

Table 2. Bioequivalence evaluation

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%
AUC (ng/ml)* (hr)	97.86	(92.67%; 103.33%)	17.178
C _{max} (ng/mL)	102.05	(94.87%; 109.77%)	23.147

CV% estimated from the Residual Mean Square

Table 3. ANOVA Results

Effects	Significant Criteria	Pharmacokinetic Parameters	
		C _{max}	AUC _t
Sequence	p<0.05	0.4959	0.6143
Period	p<0.05	0.3235	0.0091*
Treatment	p<0.05	0.6438	0.5083

Note:- * p<0.05 (significant)

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional 150 mg strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 300 mg product strength can be extrapolated to the other strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with maraviroc is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N