COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Perindopril arginine Mylan 2.5 mg, 5 mg and 10 mg, film-coated tablets (perindopril arginine)

NL/H/5535/001-003/DC

Date: 24 November 2021

This module reflects the scientific discussion for the approval of Perindopril arginine Mylan 2.5 mg, 5 mg and 10 mg, film-coated tablets. The procedure was finalised at 12 January 2011 in Poland. 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 Perindopril arginine Mylan 2.5 mg, 5 mg and 10 mg, film-coated tablets, from Mylan B.V.

The products are indicated for:

- Hypertension: treatment of hypertension.
- Heart failure: treatment of symptomatic heart failure (for 2.5 mg & 5 mg only).
- Stable coronary artery disease: reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

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

II. QUALITY ASPECTS

II.1 Introduction

Perindopril arginine Mylan 2.5 mg film-coated tablets are white, round, biconvex, film-coated tablets debossed with “PA” over “1” on one side and “M” on the other side.

Perindopril arginine Mylan 5 mg film-coated tablets are green capsule shaped, biconvex, film-coated tablets with side notch, debossed with “PA2” on one side and “M” on the other side. The tablet can be divided into equal doses.

Perindopril arginine Mylan 10 mg film-coated tablets are green, round, biconvex, film-coated tablets debossed with “PA3” on one side and “M” on the other side.

The excipients are:
tablet core - lactose monohydrate, magnesium stearate, maltodextrin, hydrophobic colloidal silica, sodium starch glycolate (type A) and povidone (K 30).

Film-coating
2.5 mg product – partly hydrolysed polyvinyl alcohol, titanium dioxide (E171), talc (E553b), lecithin (Soya) (E322), xanthan gum (E415).
5 mg and 10 mg products – partly hydrolysed polyvinyl alcohol, titanium dioxide (E171), talc (E553b), quinoline yellow aluminium lake (E104), FD & C Blue #1/Brilliant blue FCF

aluminium lake (E133), lecithin (Soya) (E322), xanthan gum (E415) and iron oxide yellow (E172).

The drug products are packed into HDPE bottles packs comprising of a white coloured HDPE bottle with a white opaque polypropylene (PP) screw cap and containing desiccant. Moreover, the drug products are packed into cold form blister packs comprising of hard tempered aluminium foil dull side lacquered and bright side PE extrusion coated and form pack laminate with desiccant layer.

II.2 Drug Substance

The active substance is perindopril arginine, an established active substance not described in the European Pharmacopoeia (Ph. Eur.). Perindopril arginine is a white to off-white or light brown coloured powder. It is sparingly soluble in water. The structure for perindopril arginine comprises of five chiral centres. The drug substance manufactured by active substance manufacturer is a single isomer controlled with specific optical rotation. Synthesis, specifications and analytical methods for the active substance are all satisfactorily described.

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.

II.3 Medicinal Product

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 are explained. The product specifications cover appropriate parameters for this dosage form. Satisfactory validation data for the analytical methods have been provided. Batch analysis results show that the finished products meet the specifications proposed. Stability studies have been carried out, which justify the proposed shelf life of the finished products of two years (after first opening of the bottle: six months) with the storage conditions: "This medicinal product does not require any special storage conditions".

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Perindopril arginine Mylan has a proven chemical-pharmaceutical quality. Information on development, manufacture and control of the drug substances and finished product have been presented in a

satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Perindopril arginine Mylan 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

Since Perindopril arginine Mylan has been shown to be essentially similar and it is assuming to be approved basing on full content of non-clinical data. Any further data were not presented and no new non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted one bioequivalence study: a single-dose, crossover study with 8 mg perindopril tablets. Based on the submitted study, Perindopril arginine Mylan 10 mg tablets are considered bioequivalent with Coversyl 10 mg tablets.

IV.2 Pharmacokinetics

Results of pharmacokinetic and statistical calculation were enclosed to the dossier of this study as well as safety data for individual subjects. The calculated confidence intervals for AUC 0-t, AUC 0-∞ and C_{max} of perindopril and perindoprilat are within the 0,80-1,25 acceptance range for bioequivalence. The extrapolated AUC is not higher than 20% in any subject (not only the mean extrapolation) for perindopril. However, a few cases of residual area values were higher than 20% observed for perindoprilate. There is no carry-over effect in the bioequivalence study and any pre-dose levels are detected.

Based on the submitted bioequivalence study Perindopril arginine 10 mg tablets are considered bioequivalent with Coversyl 10 mg tablets.

Biowaiver

The dissolution profile of Perindopril arginine tablets 2.5 mg and 5 mg against the dissolution profile of Perindopril arginine tablets 10 mg (batch used in bio-equivalence study) in three different media covering a pH range of pH 1.2 to pH 6.8 has been compared. It is stated that

more than 85% of the labelled amount of the drug is released from all tested batches in the all media and therefore, as per the provisions mentioned in CPMP *guidance on the Investigation of Bioequivalence – CPMP/EWP/QWP/1401/98-Rev 01 – Jan 2010*, the dissolution profiles can be considered as similar without any further mathematical calculations. The MAH therefore concluded that all the strengths of tested product satisfy all criteria given in CPMP guidance on bio-waiver. Therefore, the bioequivalence study results obtained on the 10 mg product can be extended to the 2.5 mg and 5 mg strengths as well.

Conclusion on bioequivalence studies

Based on the submitted bioequivalence study Perindopril arginine Mylan is considered to be bioequivalent with Coversyl.

The results of study with 10 mg formulation can be extrapolated to other strengths 2.5 mg and 5 mg, according to conditions in *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, section 4.1.6.

IV.3 Pharmacodynamics

No new data. The pharmacodynamic profile of perindopril arginine is well characterised in literature.

IV.4 Clinical efficacy and clinical safety

As perindopril arginine is a widely, long-time used, well-known active substance, the applicant has not provided additional clinical studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV.5 Risk Management Plan

The MAH has provided justification for not submitting RMP.

IV.6 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the reference product. The reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. The Authorisation of generic product is therefore linked to the 'originally' authorised medicinal product which is legally allowed as its' data protection time for the dossier has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the applied product is similar to the pharmacokinetic profile of the reference one. The generic product can be used instead of the reference one.

For this authorisation, reference is made to the clinical studies and experience with the innovator product Coversyl (Servier). No new clinical studies were conducted.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Co-Presigen, 2.5 mg/0.625 mg and 5 mg/1.25 mg film-coated tablets (perindopril arginine/indapamide), PL/H/0162-0163/001-002/DC. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

SmPC of the product has to be updated accordingly to SmPC of reference product (Coversyl).

The registration dossier of Perindopril arginine Mylan of Mylan B.V. contains adequate quality, nonclinical and clinical data and its' bioequivalence has been proven. Its' benefit/risk ratio is comparable to the reference product and therefore Perindopril arginine Mylan approval can be admitted.

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