Public Assessment Report

Scientific discussion

Myocard
Doxazosin mesilate

DK/H/1388/001/DC

This module reflects the scientific discussion for the approval of Myocard. The procedure was finalised at 16-01-2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This generic application for marketing authorisation in accordance with article 10(1) of Directive 2001/83/EC as amended concerns Myocard, Prolonged-release tablets 4mg, approved in a Decentralised Procedure on 16th January 2009. The concerned member states were CZ, EE, EL, FR, HU, IE, LT, LV, NL, NO, PL, PT, RO and UK.

Essential similarity is claimed with the innovator product Carduran tablets 4 mg, Pfizer ApS., which was first authorised in Denmark on April 2, 1987.

Therapeutic indications are essential hypertension and symptomatic treatment of benign prostatic hyperplasia.

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form: Prolonged-release tablet.
Active substance: doxazosin mesilate
Strength: containing 4,85 mg doxazosin mesilate, corresponding to 4 mg doxazosin.
Excipients: Tablet core: Polyethylene oxide, Microcrystalline cellulose, Povidone, Butylhydroxytoluene, α-Tocopherol, Colloidal anhydrous silica, Sodium stearyl fumarate, Film-coating**:** Methacrylic acid – ethyl acrylate copolymer, Colloidal anhydrous silica, Macrogol, Titanium dioxide (E171).
Shelflife: 5 years.
Special precautions for storage: None
Nature and content of container: 14, 15, 28, 30, 50 x 1, 60, 90, 100 tablets in PVC/PVDC aluminium blisters.

II.2 2.2 Drug Substance

The drug substance doxazosin mesilate is described in Ph. Eur. Two suppliers of the drug substance are proposed. The documentation on the drug substance is provided as Drug Master Files (DMFs) from each of the ASMs.
Both the ASMs use methanol in the last step of the synthesis of doxazosin mesilate, which gives rise to a possible formation of the highly toxic alkyl mesilates. A limit for alkyl mesilates has been included in the specification of one of the ASM, and a justification for the absence of control of alkyl mesilates in the drug substance has been given by the applicant.
The control tests and specifications for drug substance product are adequately drawn up in each of the DMFs and by the finished product manufacturer.

In each of the DMFs stability studies have been performed with the drug substance. No significant changes in any parameters were observed.
The proposed retest period of 5 years respectively 12 months with no special precautions for storage for the drug substance is justified.

II.3 Medicinal Product

The development of the product has been adequately described, the choice of excipients is justified and their functions explained. All excipients are well known and commonly used in pharmaceutical formulations. The dissolution testing method is adequate and comparative dissolution profiles have

been presented between the formulation applied for, including the test biobatches, and the brand leader/ reference product.

The manufacturing process is a standard wet granulation process and it has been sufficiently validated on pilot scale and production scale batches.

The product specifications cover appropriate parameters for this dosage form. The possibility of formation of alkyl mesilate esters has been addressed. Validations of the analytical methods have been presented. Batch analysis has been performed on 4 pilot and 4 commercial scale batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 5 years with no special storage conditions for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Doxazosin are well known. As Doxazosin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Doxazosine is a well known and widely used active substance. This is a generic application and no new indications are added. The applicant has not provided additional studies apart from bioequivalence studies, and this is acceptable to the RMS.

IV.2 Pharmacokinetics

Following oral administration doxazosin is rapidly absorbed and has a mean bioavailability of 65 to 70%.
Doxazosin is available on the market as immediate release tablets, or as a controlled release formulation containing 4 mg doxazosin. This formulation functions on the basis of osmotic pressure, releasing the drug at zero-order (osmotic tablets). A characteristic for this tablet is the relative long lag phase of 2 - 4 hours (in vitro), followed by constant zero-order release of more than 24 hours. In vivo tmax occurs at 10-15 hours after dosing, whereas Cmax amounts to 6-8 ng/nl. A plateau is maintained for several hours.

Following i.v. or oral administration doxazosin is extensively metabolised in the liver, primarily by O-demethylation of the quinazoline substituent or hydroxylmethylation of the benzodioxan moiety. The primary metabolites are 6-O-desmethyl- and 7-O-desmethyl-doxazosin, which account for 16% and 7% of an administered dose respectively. 6'-hydroxy- and 7'-hydroxy-doxazosin account for 5% and 7% of the other major metabolites respectively. Minor metabolites include 2-aminoand 2-piperazinyldoxazosin. Pharmacologically active metabolites have not been detected In health subjects the terminal elimination half-life has been reported to be 9.4 h following i.v. administration. Following oral administration elimination half-lives of 16-22 hours have been reported.

IV.3 Bioequivalence

To support the application, the applicant has submitted as report 2 bioequivalence studies.

Study 1 was a 2-period combined single-dose (fasting) and multiple-dose (fasting and fed) crossover study. 24 (+4 standby) subjects were included in the study. The first 24 subjects who completed the study were, as per protocol, included in the pharmacokinetic and statistical analysis.
In the multiple dose phase of the study under both fasting and fed conditions the 90% CI for C_{max}, C_{min} and AUC_{τ} were within the 80-125% acceptance range. A slightly higher C_{max} was seen for the test product in the fed state than in the fasting state; however, since the 90% CI for AUC and C_{max} for the comparison of fed and fasting conditions was within 80-125%, the food effect can be disregarded.
In the single dose phase of the study the 90% CI for AUC_{∞} (0.82-0.91) and AUC_t (0.80-0.91) was within the 80-125% acceptance range, whereas for C_{max} a lower level was found for the test product (7.18 ng/ml) than for the reference product (10.2 ng/ml), which was also reflected in the 90% CI for C_{max} (0.63-0.79). The peak plasma concentration are considered of less relevance for the efficacy of the product and the single dose administration was not to be considered for the conclusion of bioequivalence; anyway an additional single-dose bioequivalence study was performed in order to confirm the bioequivalence between the formulations after single-dose administration.

Study 2 was 2-period single dose crossover bioequivalence study conducted under fasting conditions. As per protocol the first 24 subjects who completed the study were included in the pharmacokinetic and statistical analysis.

The 90% confidence intervals calculated for AUC_{0-t} (90.24-121.58%) and $AUC_{0-\infty}$ (90.18-120.08%) and the mean peak plasma concentration C_{max} (92.58-123.09%) were within the acceptance range of 80-125% after single dose administration.

IV.4 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further of such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Myocard, Prolonged-release tablets 4mg are recommended for approval.

Area[1]	**Description**
Quality	Stability data of commercial scale batches manufactured with drug substance from Chemische Fabrik Berg will be submitted, when available.
Quality	The enclosed stability studies will be continued.

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance