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IRISH MEDICINES BOARD

**PUBLIC ASSESSMENT REPORT FOR A
MEDICINAL PRODUCT FOR HUMAN USE**

Scientific discussion

Farmadura XL 4mg & 8mg Prolonged Release Tablets
DOXAZOSIN
PA0822/023/001 & 002

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Farmadura XL 4mg and 8mg prolonged release tablets from Pfizer healthcare Ireland on 11th March 2011 for the treatment of hypertension and can be used as a sole agent to control blood pressure in hypertensive patients.

In patients inadequately controlled on single antihypertensive therapy, Farmadura XL may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application.

This means that the Marketing Authorisation Holder for Cardura XL, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Farmadura XL. Farmadura XL has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Cardura XL.

The Summary of Product Characteristics (SPC) for this medicinal product is available on the IMB's website at www.imb.ie.

Name of the product	Farmadura XL 4mg & 8mg Prolonged Release Tablets
Name(s) of the active substance(s) (INN)	DOXAZOSIN
Pharmacotherapeutic classification (ATC code)	C02CA04
Pharmaceutical form and strength(s)	4mg & 8mg Prolonged Release Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA822/23/1-2
Marketing Authorisation Holder	Pfizer Healthcare Ireland

II QUALITY ASPECTS

II.1 Introduction

This application is for Farmadura XL 4mg and 8mg prolonged release tablets.

II.2 Drug substance

The active substance is doxazosin, a established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided in the dossier for Cardura XL PA 822/4/1-2.

II.3 Medicinal product

P.1 Composition

The product are formulated as prolonged -release tablets containing either 4 mg or 8 mg of doxazosin (as mesilate). Tablets also contain the following excipients:

Polyethylene oxide, Sodium chloride, Hypromellose, Red ferric oxide (E172), Titanium dioxide (E171), Magnesium stearate, Cellulose acetate, Macrogol, Pharmaceutical glaze, Black iron oxide (E172), Ammonium hydroxide and Propylene glycol. This is the same as for Cardura XL PA 822/4/1-2.

P.2 Pharmaceutical Development

The product, the established pharmaceutical form and its development is adequately described in dossier for Cardura XL PA 822/4/1-2 in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guideline and the process is considered to be sufficiently validated. The data is provided in dossier for Cardura XL PA 822/4/1-2.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications. The data is provided in dossier for Cardura XL PA 822/4/1-2.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data. The data is provided in dossier for Cardura XL PA 822/4/1-2.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented in Aluminium foil/aluminium foil blister strips in a carton.

Evidence has been provided that blister material complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

The data is provided in dossier for Cardura XL PA 822/4/1-2.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years when stored in the original package below 30°C. The data is provided in dossier for Cardura XL PA 822/4/1-2.

Adventitious Agent Safety

The data is provided in dossier for Cardura XL PA 822/4/1-2.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been cross-referenced to the dossier of already authorised/approved medicinal products Cardura XL 4mg and 8 mg prolonged release tablets assuring consistent quality of Farmadura XL 4mg and 8 mg prolonged release tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Cardura XL on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

Preclinical data reveal no special hazard for humans based on conventional animal studies in safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

Doxazosin crosses the placenta. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses.

These doses were approximately 300 times the maximum recommended human dose.

Doxazosin is contraindicated during lactation as animal studies have shown that doxazosin accumulates in milk of lactating rats.

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. The product information is the same as the innovator Cardura XL.

IV CLINICAL ASPECTS**IV.1 Introduction**

Doxazosin is a well known active substance with established efficacy and tolerability.

This medicinal product is the same as on the European market.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Cardura XL marketed by Pfizer.

IV.2 Pharmacokinetics

Absorption: After oral administration of therapeutic doses, Farmadura XL is well absorbed with peak blood levels gradually reached at 8 to 9 hours after dosing. Peak plasma levels are approximately one third of those of the same dose of immediate release Cardura tablets. Trough levels at 24 hours are, however, similar.

The pharmacokinetic characteristics of Farmadura XL will lead to a smoother plasma profile. Peak/trough ratio of Farmadura XL is less than half that of immediate release Cardura tablets. At steady-state, the relative bioavailability of doxazosin from Farmadura XL compared to the immediate release form was 54% at the 4mg dose and 59% at the 8mg dose.

Pharmacokinetic studies with Farmadura XL in the elderly have shown no significant alterations compared to younger patients.

Biotransformation / Elimination: The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basis for once daily dosing. Doxazosin is extensively metabolised with <5% excreted as unchanged drug.

Pharmacokinetic studies with immediate release doxazosin in patients with renal impairment also showed no significant alterations compared to patients with normal renal function.

There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 patients with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a decrease in apparent oral clearance of 30%. (See also 4.4 Special warnings and special precautions for use). Approximately 98% of doxazosin is protein-bound in plasma.

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

Absorption and bioavailability, distribution, metabolism, elimination, dose proportionality and time dependence, target/special populations, interactions, relationship between concentration and effect are the same as the marketed Innovator Cardura XL.

IV.3 Pharmacodynamics

Doxazosin is a potent and selective post-junctional alpha 1-adrenoceptor antagonist.

Administration of Farmadura XL to hypertensive patients causes a clinically significant reduction in blood pressure as a result of a reduction in systemic vascular resistance. This effect is thought to result from selective blockade of the alpha-1 adrenoceptors located in the vasculature.

With once daily dosing, clinically significant reductions in blood pressure are present throughout the day and at 24 hours post dose.

The majority of patients are controlled on the initial dose. In patients with hypertension, blood pressure during treatment with Farmadura XL was similar in both the supine and standing position.

Responder data from the 2 primary hypertension efficacy studies (including a total of 630 doxazosin treated patients) indicate that those patients controlled on 1mg, 2mg or 4mg doxazosin immediate release tablets would be equally well controlled on 4mg Farmadura XL.

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with coexistent diabetes mellitus, gout and insulin resistance. Doxazosin is suitable for use in patients with coexistent asthma, left ventricular hypertrophy and in elderly patients. Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator. Additionally, doxazosin improves insulin sensitivity in patients with impairment. Doxazosin produces favourable effects on blood lipids, with a significant increase in the HDL/total cholesterol ratio and trends to a favourable reduction in total triglycerides. It therefore confers an advantage over diuretics and beta adrenoceptor blocking agents which adversely affect these parameters. Based on the established association of hypertension and blood lipids with coronary heart disease, the favourable effects of doxazosin therapy on both blood pressure and lipids indicate a reduction in risk of developing coronary heart disease.

IV.4 Clinical Efficacy

No difference in efficacy is expected from the reference product Cardura XL as it is an informed consent application. No additional studies have been conducted as they are not necessary.

IV.5 Clinical Safety

No difference in safety is expected from the reference product Cardura XL as it is an informed consent application. No additional studies have been conducted as they are not necessary.

The schedule for Periodic Safety Update Reports (PSUR) submission should be every 3 years.

Pharmacovigilance System

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance system, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

As this is an informed consent application, efficacy and safety is the same as the innovator product Cardura XL which is currently marketed.

No additional safety or efficacy studies are necessary for this application.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Farmadura XL 4mg & 8mg Prolonged Release Tablets is the same as Cardura XL 4mg and 8mg prolonged release tablets. Doxazosin is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The IMB, on the basis of the data submitted considered that Farmadura XL 4mg & 8mg Prolonged Release Tablets is the same as the reference product and therefore granted a marketing authorisation.

VI REVISION DATE

March 2011