

PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Doxazosin Disphar 2 and 4, tablets, 2 and 4 mg
Disphar International B.V., The Netherlands

Doxazosin mesilate

This assessment report is published by the MEB following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/0811/01-02/MR
Registration number in the Netherlands: RVG 31675 and 31676**

6 January 2008

Pharmacotherapeutic group:	Urologica, antihypertensiva
ATC code:	C02CA04, G04CA
Route of administration:	oral use
Therapeutic indication:	- Essential hypertension; - Clinical symptoms of benign prostatic hyperplasia (BPH) prescription only
Prescription status:	
Date of first authorisation in NL:	4 October 2004
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)
Concerned Member States:	IT

For product information for healthcare professionals and users, including information on pack sizes and presentations see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the MEB has granted a marketing authorisation for Doxazosin Disphar 2 and 4, tablet 2 and 4 mg from Disphar International B.V./NL. The first date of authorisation was on 4 October 2004 in the Netherlands. The product is indicated for treatment of essential hypertension and treatment of clinical symptoms of benign prostatic hyperplasia (BPH).

A comprehensive description of the indications and posology is given in the SPC.

Doxazosine is a quinazoline-based highly selective postsynaptic alpha-1-adrenoreceptor antagonist. It blocks alpha-1-adrenoreceptor in the arterioles and veins which leads to a fall in peripheral vascular resistance and in venous return to the heart. Doxazosine also blocks the alpha-1-adrenoreceptors in the trigone muscle of the bladder the urethra. These receptors contribute to the resistance to outflow of the bladder. Doxazosine can reduce this resistance and improve the outflow of urine from the bladder. This is the background for the use of doxazosine and other alpha-1-adrenoreceptor antagonists in hypertension and benign prostatic hyperplasia.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC .

This application concerns a generic application claiming essential similarity with the innovator product Carduran® which has been registered in Denmark by Pfizer since 1989 (original product). In addition, reference is made to Cardura ® authorisations in the individual Member States (reference product). This type of application refers to information that is contained in pharmacotoxicological and clinical part of the dossier of the authorisation of the reference product. A reference product 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. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Cardular Uro® 4 mg, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients

The active substance doxazosin mesilate is a well-known substance. 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 to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance use in the medicinal product.

The production process has been adequately described. The active substance specification is considered adequate to control the quality. Stability data on the active substance(s) have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 36 months when stored at 25 °C.

Medicinal Product

Composition

Doxazosin Disphar 2 and 4 mg are tablets. Each tablet contains 2.425 mg or 4.85 mg doxazosin mesilate, respectively, corresponding to 2 mg or 4 mg doxazosin. The excipients are microcrystalline cellulose anhydrous lactose, sodium starch glycolate, colloidal anhydrous silica, sodium lauryl sulphate and magnesiumstearate.

All the excipients are well known in pharmaceutical products and are described in the European Pharmacopoeia (Ph.Eur). The Ph.Eur is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

The tablets are packaged in PVC/PVdC blister, heat-sealed by a sheet of aluminium foil.

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The purpose was to develop tablets bioequivalent to the reference product Cardular Uro® 4 mg tablets of Pfizer GmbH, registered in Germany. Several developmental trials were performed, concerning granulation and compression, leading to the current composition and method of preparation. Dissolution was compared with this reference product.

The tablets have a score line. They are easy to break by hand and breakability fulful the requirements of the Ph.Eur.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form, and include tests for appearance, identity, purity, uniformity of weight, dissolution, hardness, friability, related substances, and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the three production batches of each strength at one site and two production batches of another site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product

Stability data on the product have been provided for three batches of each strength in accordance with applicable European guidelines demonstrating the stability of the product for 5 years in

PVC/PVdC/Aluminium blister. Due to the low hardness of the tablets at 40°C/75% RH the storage condition (do not store above 30°C) is justified.

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.2 Non clinical aspects

This product is a generic formulation of Carduran® which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of doxazosin released into the environment. It does not contain any component which result in additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Carduran® marketed by Pfizer.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product Cardular 4 mg from Pfizer, Germany.

The first bioequivalence study was submitted in the original application. Bioequivalence of doxazosin from the 4 mg tablet to be registered was proven with Cardular 4 mg from Pfizer, Germany. In 2003, the CRO, which performed this bioequivalence study was compromised. During an inspection it was found that a significant proportion of data mentioned in the study reports were based on data that are considered to be incorrect and incomplete, e.g. the correspondence between raw and reported data was not acceptable. Therefore, the applicant was asked to either justify the existing results or perform repeat studies of Doxazosin.

A new bioequivalence study was submitted in which the Doxazosin PCH 4 mg tablets, are compared with Cardular Uro® 4 mg (Pfizer, Germany) to prove that both products can be considered bioequivalent. The study is performed by another well known CRO

This study was conducted as an open randomised, single dose crossover study. Twenty-four healthy volunteers, 12 females and 12 males, aged 19-35 years, were included in this study. Each subject received a single dose (4 mg) of one of the 2 doxazosin formulations in fasted state. For each subject there were two dosing periods, separated by a washout period of at least one week. The following formulations were administered:

The reference tablet is marketed in Germany. The test tablet is identical to the tablet to be registered. The tablets were administered with 200 ml water after 10 hours fasting. Blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of the products. Plasma samples were analysed for doxazosin by HPLC with fluorescence detection. The concentration range for the calibration curves was 1.0-100 ng/mL doxazosin in plasma. The lower limit of quantification was 1.0 ng/mL. The method was validated and a validation report was provided. The pharmacokinetic variables were estimated model independently and statistical analysis was carried out on the ln-transformed data using ANOVA.

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). The report is of good quality.

Results

A total of 23 volunteers completed both study periods. One volunteer was withdrawn at the start of the second period for safety reasons (systolic blood pressure at standing < 100 mmHg prior to trial medication intake).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	432 \pm 86	481 \pm 116	35 \pm 7	1.0(1.0-5) *	15 \pm 3
Reference	426 \pm 77	471 \pm 99	34 \pm 6	1.0(1.0-2.5) *	14 \pm 3
*Ratio (90% CI)	1.01 (0.96-1.06)	1.02 (0.97-1.07)	1.01 (0.96-1.05)	1.0	
CV (%)	9.8	10.3	9.0		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
 AUC_{0-t} area under the plasma concentration-time curve over the dosing interval
 C_{max} maximum plasma concentration
 T_{max} time for maximum concentration
 $T_{1/2}$ half-life

*In-transformed values

Conclusion

Based on pharmacokinetic variables of doxazosin it can be concluded that the tested Doxazosin 4 mg tablets are bioequivalent to the Cardular Uro® 4 mg (Pfizer, Germany). The calculated 90% confidence intervals for AUCinf., $AUC(0-t)$ and C_{max} are in agreement with those calculated by the applicant and are within the acceptance range of 0.80 – 1.25. Also the other pharmacokinetic variables are comparable between the test product and the reference product.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Readability test

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed.

Risk Management Plan

Doxazosin was first approved in 1987 in Denmark, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of doxazosin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

The first PSUR will cover a 3 year period starting from 25 August 2006 (day 90 of the Mutual Recognition Procedure). The second PSUR will cover a 2 year period to coincide with the renewal. Hereafter, the

PSURs will be submitted three-yearly. The MAH should submit the PSURs within 60 days from the data lock point.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Doxazosin Disphar 2 and 4, tablet 2 and 4 mg is a generic form of Carduran® which is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the European guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The Board In the Netherlands followed the advice of the assessors.

On the basis of the data submitted, the MEB considered that Disphar had demonstrated bioequivalence for Doxazosin Disphar 2 and 4 with the reference product and has therefore granted a marketing authorisation.

The Member States mutually recognised the Dutch evaluation of the marketing authorisation. There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	Britisch Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{\max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products, CMD(h),
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{\frac{1}{2}}$	Half-life
t_{\max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States