COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Doxazosine retard CF 4 mg, prolonged-release tablets
(doxazosin mesilate)

NL/H/4618/001/DC

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This module reflects the scientific discussion for the approval of Doxazosine retard CF 4 mg, prolonged-release tablet. The procedure was finalised on 28 June 2006 in Sweden (SE/H/469/001/MR). After a transfer on 03 January 2007, the current RMS is the Netherlands. 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
MRP	Mutual Recognition Procedure
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Doxazosine retard CF 4 mg, prolonged-release tablet, from Centrafarm B.V.

The product is indicated for the treatment of essential hypertension and clinical symptoms of benign prostate hyperplasia.

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 Cardular PP which has been registered in Germany by Pfizer GmbH, and Alfadil 4 mg prolonged release tablets registered in Sweden by Pfizer GmbH. Three bioequivalence studies were submitted in support of this application. Since a potential serious risk to public health concern regarding bioequivalence was raised by two CMS at day 90 of the MR-procedure, a CMD referral procedure was initiated. Day 60 of the CMD(h) procedure was on 03 March 2006, and since there could be no agreement the procedure was referred to the CHMP. A positive opinion was adopted by CHMP on 28 June 2006.

The reference member state (RMS) of the initial procedure was Sweden. The role of RMS was transferred to the Netherlands on 12 September 2018.

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

I. QUALITY ASPECTS

I.1 Introduction

Doxazosine is presented in the form of prolonged-release tablets containing 4.85 mg of doxazosin mesilate which corresponds to 4 mg of doxazosin. The formulation is composed of the core excipients polyethylene oxide, microcrystalline cellulose, povidone, all-rac-α-tocopherol, colloidal anhydrous silica and sodium stearyl fumarate, and the coating excipients methacrylic acid - ethyl acrylate copolymer (1:1), colloidal anhydrous silica, macrogol and titanium dioxide. The tablets are packed in PVC/PVDC/Al-blisters.

I.2 Drug Substance

Doxazosin mesilate has a monograph in the Ph Eur. Information on Doxazosin mesilate has been supplied in the form of an ASMF.

Doxazosin mesilate is a white to almost white crystalline powder, which is slightly soluble in methanol and water, soluble in tetrahydrofuran/water 35:15, and practically insoluble in acetone. The structure of doxazosin mesilate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on e.g. chirality and polymorphism is presented.

Manufacturing process
The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Quality control of drug substance
The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability of drug substance
Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

I.3 Medicinal Product

Pharmaceutical development
The product development has taken into consideration physico-chemical characteristics of the active substance such as particle size, dissolution properties, bioequivalence, and formulation stability.

Manufacturing process
The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

Control of excipients
Doxazosine retard CF 4 mg is formulated using excipients described in the current Ph Eur, except for metacrylic acid-ethyl acrylate copolymer and polyethylene oxide which are controlled according to acceptable USP/NF and in house specifications, respectively.

Quality control of drug product
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability of drug product
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with no special storage precautions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

All raw materials used in the product are either of non-animal origin and/or out of the scope of the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

II. NON-CLINICAL ASPECTS

II.1 Discussion on the non-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 preclinical data, no further non-clinical data have been submitted or are considered necessary.

III. CLINICAL ASPECTS

III.1 Pharmacokinetics

Following oral administration of conventional tablets, doxazosin is rapidly absorbed and has a mean bioavailability of 65 to 70% in healthy male volunteers. Compared with the standard formulation the relative bioavailability of the 4 mg prolonged-release formulation is about 54%. Characteristic for the originator prolonged release tablet formulation is the lag phase of about 2 hours, followed by a constant zero-order release of doxazosin over a period of 12 hours. *In vivo* a plateau concentration is reached 4-8 hours after dosing. Cmax of the 4 mg formulations amounts to about 10 ng/ml. The plateau is maintained for several hours. The apparent terminal elimination half-life is about 16 hours. Due to the lack of a pronounced peak, especially with multiple dose administration, doxazosin from this formulation is better tolerable than instant release forms. Doxazosin is extensively metabolised in the liver, primarly by O-demethylation of the quinazoline substituent or hydroxymethylation of the benzodioxan moiety. Pharmacologically active metabolites have not been detected.

Bioequivalence studies

Three bioequivalence studies were submitted in support of this application. The reference products used in the bio-equivalence studies are Cardular PP 4 mg tablet marketed by Pfizer GmbH in Germany, Diblocin PP 4 mg prolonged release tablets marketed by AstraZeneca in Germany, and Cardura XL 4 mg prolonged release tablets manufactured by Pfizer and marketed in UK.

Study 1. The first study was conducted at Avoxova Ltd., Warsaw, Poland in December 2000 - February 2001.

Study 2. During the evaluation period, the GCP compliance of Avoxova was questioned and the applicant conducted an additional bioequivalence study of identical design. The new bioequivalence study was performed in November - December 2002 at Vimta Labs Limited, Hyderabad, India (study number 5208/02-03).

Study 3. An additional single dose bioequivalence study was submitted to support bioequivalence after single dose administration. The bioequivalence study was performed in June-July 2004 at Vimta Labs Limited, Hyderabad, India (study number 1995/04-05).

GCP
Vimta Labs Limited, Hyderabad, India including doxazosin studies 5208/02-03 and 1995/04-05 have been inspected by a joint inspection team from Denmark, Sweden and Portugal and was found to be in compliance with GCP.

Study 1 (Avoxova study)
Design study
Employed the same design as study 2.

Results
Results in study 1 were similar to those of study 2, except that bioequivalence was demonstrated between test and reference after single dose administration. Results from the Avoxova study were not taken into account in approval of the product as the GCP compliance of the CRO where this study was conducted was questioned.

Study 2 (study nr. 5208/02-03)
Design study
The relative bioavailability of doxazosin 4 mg in a new prolonged-release formulation (Cimex Development AG) compared with Diblocin PP 4 mg tablets (AstraZeneca), was determined in a randomised, 2-period cross-over combined single and multiple dose bioequivalence study in healthy volunteers. On day 1, one tablet containing 4 mg doxazosin was given as a single dose after an overnight fast. After the single dose phase subjects received for 6 days (day 4-9) once daily doses of doxazosin. On Day 9, the tablets were taken 15 min. after intake of a standardised high calorie, high fat breakfast. Blood samples were collected repeatedly up to 72 hours after drug administration on Day 1, for 24 h on Day 8 and for 48 h after the dose on Day 9.

Results
The results of are given in the following tables as geometric mean (CV%) with the exception of t_{max}, which is given as median (range).

Table 1. Single dose (day 1)

Preparation	C_{max} (ng/mL)	t_{max} (h)	AUC_t (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)
Test	7.18 (25)	12 (8 – 24)	232 (31)	258 (33)
Reference	10.8 (35)	12 (8 – 14)	268 (41)	288 (41)
Ratio test/ref	0.70		0.87	0.90
(90% CI)	(0.62-0.79)		(0.78-0.96)	(0.80-1.00)

Table 2. Multiple dose fasted (day 8)

Preparation	C_{max} (ng/mL)	C_{min} (ng/mL)	t_{max} (h)	AUC_{0-24h} (ng*h/mL)
Test	15.4 (33)	9.32 (45)	6 (4 – 14)	287 (34)
Reference	17.5 (34)	10.13 (39)	10 (6 – 16)	319 (35)
Ratio test/ref	0.88	0.92		0.90
90% CI	0.82 – 0.95	0.81 – 1.04		0.83 – 0.98

Table 3. Multiple dose fed (day 9)

Preparation	C_{max} (ng/mL)	C_{24h} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng*h/mL)
Test	19.8 (36)	10.5 (36)	9 (5 – 12)	323 (32)
Reference	18.8 (33)	10.9 (31)	9 (5 - 14)	326 (29)
Ratio test/ref	1.05	0.96		0.99
90% CI	0.93 – 1.18	0.87-1.07		0.91 – 1.08

Table 4. Effect of food on the test preparation (day 9/day 8)

Preparation	C_{max} (ng/mL)	C_{24h} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng*h/mL)
Fed	19.8 (36)	10.5 (36)	9 (5 – 12)	323 (32)
Fasted	15.4 (33)	9.32 (45)	6 (4 – 14)	287 (34)
Ratio test/ref	1.28	1.13		1.12
90% CI	1.16 – 1.42	1.01-1.26		1.04 – 1.22

Table 5. Effect of food on the reference preparation (day 9/day 8)

Preparation	C_{max} (ng/mL)	C_{24h} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng*h/mL)
Fed	18.8 (33)	10.9 (31)	9 (5 - 14)	326 (29)
Fasted	17.5 (34)	10.13 (39)	10 (6 – 16)	319 (35)
Ratio test/ref	1.08	1.08		1.02
90% CI	0.98-1.19	0.96-1.20		0.95-1.11

Study 3 (study nr. 1995/04-05)

Design study

The relative bioavailability of doxazosin 4 mg prolonged-release tablet (Cimex Development AG) compared with Cardura XL 4 mg tablets (Pfizer), was determined in a randomised, 2-period cross-over single dose bioequivalence study in healthy volunteers. Blood samples were collected up to 72 hours post administration.

Results
The pharmacokinetic results for the test product and for the reference product are given in the table below.

Table 6. Pharmacokinetic parameters for test and reference given as geometric mean (CV%) with the exception of t_{max}, which is given as median (range). n=24.

Preparation	C_{max} (ng/mL)	t_{max} (h)	AUC_t (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)
Test	8.9 (31)	10 (4 - 24)	264 (29)	286 (30)
Reference	8.4 (27)	12 (8 – 24)	252 (37)	275 (39)
Ratio test/ref (90% CI)	1.07 (0.93-1.23)		1.05 (0.90-1.226)	1.04 (0.90-1.20)

Conclusion on bioequivalence studies:
At steady state, the test preparation showed bioequivalence with the reference preparation in terms of rate and extent of absorption in a fasting state and after intake with food. Bioequivalence was shown after single dose administration in study 3 (1995/04-05), but not in study 2 (5208/02-03).

During the MR procedure, questions were raised regarding the lack of bioequivalence after single dose administration in one of the two studies, tendency for shorter t_{max} for the test product, observed food effect for test product and deviation from guideline regarding evaluation of food effect. As these issues could not be resolved during the MRP, a CMD(h) referral followed the mutual recognition procedure. In response to the questions raised in the CMD(h) procedure, the applicant provided an extensive response, including data from an additional pilot bioequivalence study demonstrating bioequivalence after single dose administration. Agreement could not be reached within the CMD(h) procedure, and these issues were further discussed within CHMP. The CHMP concluded that bioequivalence was sufficiently established. The observed differences in t_{max} are modest and the C_{max} of the test tablet is not higher than the innovator tablet. It is unlikely that these differences will result in clinically relevant adverse events. Sufficient reassurance has been provided that the steady state results submitted are representative of other batches.

The food-interaction study was not performed according to the CHMP guidelines. The applicant has not been able to justify the chosen study design to evaluate the food effect. As there is a small food effect on AUC, and the evaluation was made before a new steady state was reached, the food effect is likely underestimated in the conducted study. The underestimation is however, likely quite low, and the true food effect is most likely not clinically relevant. Bioequivalence has been demonstrated between test and reference both in a fasting state and with food at steady state. Although there might be a slightly higher influence of food on the test than on the reference, there are no clinically relevant differences between test and reference either in fasted or in fed state. The effect of food is unlikely to have any clinical consequences.

III.2 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 clinical data have been submitted or are considered necessary.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed.

The risk/benefit ratio is considered positive and Doxazosine retard CF 4 mg, prolonged-release tablet is recommended for approval.

The MAH will provide PSURs according to normal procedures. In addition to this, a commitment has been made to provide Overall Safety Reports (OSR) for Doxazosine retard CF 4 mg, prolonged-release products manufactured by Cimex development, Switzerland, once every six months during the first 2 years after end of the CMDh procedure. The OSR will specifically address any potential signals of problems with interchangeability.

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
NL/H/4618/ 001/II/022	Update of the ASMF of the active ingredient manufacturer.	No	26-4-2019	Approved	N/A
NL/H/4618/ 001/IA/023	Deletion of the manufacturing sites for active substance.	No	25-6-2019	Approved	N/A
NL/H/4618/ 001/IB/024	Adapted SmPC and PL to excipients guideline and editorial changes to labelling.	Yes	18-12-2019	Approved	N/A
NL/H/4618/ IB/025/G	Changes in: - primary and secondary packaging sites - type of container - pack size of the finished product	Yes	8-10-2020	Approved	N/A
NL/H/4618/ 001/IA/026/ G	- Change in the address of the marketing authorisation holder -Replacement of a manufacturer responsible for batch release. Not including batch control/testing.	Yes	26-1-2022	Approved	N/A
NL/H/4618/ 001/IB/027	Change in the specification parameters and/or limits of the finished product for release and shelf life.	No	5-9-2022	Approved	N/A