LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Doxazosin NM Pharma
4 mg prolonged-release tablet
(Doxazosin mesilate)

SE/H/465/01

This module reflects the scientific discussion for the approval of Doxazosin NM Pharma 4 mg prolonged-release tablets. The procedure was finalised at March 31st 2006. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

EnaPharm AB has applied for a marketing authorisation for Doxazosin NM Pharma 4 mg prolonged-release tablet claiming essential similarity to Cardular PP 4 mg prolonged-release tablet marketed in Germany by Pfizer GmbH. The product contains doxazosin mesilate as active substance and is indicated for the treatment of essential hypertension and clinical symptoms of benign prostate hyperplasia. The reference products used in the bio-equivalence studies were Diblocin PP 4 mg prolonged-release tablet marketed in Germany by AstraZeneca GmbH (study 5208/02-03) and Cardura XL 4 mg prolonged-release tablet marketed in the UK by Pfizer Ltd (study 1995/04-05).

Since a major health concern regarding bioequivalence was raised by a CMS at day 90 of the MR-procedure, a CMD referral procedure was initiated. After having received additional information from the Company and a commitment to perform post marketing surveillance, the bioequivalence issue was considered solved and the MR-procedure thus successfully concluded.

II. QUALITY ASPECTS

II.1 Introduction

Doxazosin NM Pharma is presented as prolonged-release tablets containing doxazosin mesilate 4.85 mg corresponding to 4 mg doxazosin. The excipients of the formulation are polyethylene oxide, microcrystalline cellulose, povidone, all-rac-α-tocopherol, colloidal anhydrous silica, sodium stearyl fumarate, butylhydroxytoluene (E321), methacrylic acid - ethyl acrylate copolymer, macrogol, and titanium dioxide (E171). The tablets are packed in PVC/PVDC/Al-blisters.

II.2 Drug Substance

At the time of first approval, no PhEur monograph was available for the drug substance doxazosin mesilate. Information on doxazosin mesilate has been supplied in the form of ASMFs (active substance master files).

Doxazosin mesilate is a white to almost white, crystalline powder which is practically insoluble in acetone, ethyl acetate, isopropyl alcohol, and hexane, and slightly soluble in methanol and water. The structure of doxazosin mesilate has been adequately proven and its physico-chemical properties are sufficiently described. Relevant information regarding polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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 studies under ICH conditions have been conducted and the stability data presented support the proposed re-test period.

II.3 Medicinal Product

Doxazosin NM Pharma 4 mg prolonged-release tablet is formulated using excipients described in the current PhEur, except for polyethylene oxide and methacrylic acid - ethyl acrylate copolymer which are controlled according to USP/NF. No raw material of animal origin has been used in the manufacture of this product.

Taken into consideration during product development was e.g. choice and optimisation of the formulation, optimisation of the dissolution test and *in-vitro* dissolution rate, and formulation stability.

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.

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 studies under ICH conditions have been performed and the stability data presented support the shelf life stated in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.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-clinicl data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.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. C_{max} 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.

Three bioequivalence studies were submitted in support of this application.

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 design
Study 2
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 bioeuivalence 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.

Study 1 employed the same design as study 2.

Study 3 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
Study 2 (5208/02-03)
The results are given in the following table 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)**	**$AUC_{0-¥}$ (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 1 (Avoxova study)
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. However, these data were considered as supportive.

Study 3 (study 1995/04-05)
The pharmacokinetic results for the test product and for the reference product are given in the table below.

Table 1 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)	$AUC_{0-¥}$ (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	1.07		1.05	1.04
(90% CI)	(0.93-1.23)		(0.90-1.226)	(0.90-1.20)

Discussion

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 1995/04-05, but not in study 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. Although there is no mechanistic explanation, it seems reasonable to conclude that the lower C_{max} observed after single dose administration in study 5208 is an isolated observation. A potentially slightly lower C_{max} after the first dose and a small difference in t_{max} does not constitute any safety concern. It was concluded that there are no clinically relevant differences in absorption rate between test and reference formulations.

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. In a fasting state, the PK parameters for test are 8-12% lower than for reference and in the fed state between 4% lower and 5% higher. Hence, although there might be a slightly higher influence of food on the test than on reference, there are no clinically relevant differences between test and reference either in fasted or in fed state.

With commitment from the company for additional post-marketing surveillance, the CMD referral was positively ended and approval could be granted.

IV.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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Doxazosin NM Pharma 4 mg prolonged release tablet is recommended for approval.

The company will provide PSURs according to normal procedures. In addition to this, a commitment has been made to provide Overall Safety Reports (OSR) for Doxastad 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.