Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Doxazosin mesilate
Cardura

UK/W/0077/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	19 January 2015

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Doxazosin mesilate
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	C02CA04
Pharmaceutical form(s) and strength(s):	1, 2, 4, and 8 mg tablets

I. EXECUTIVE SUMMARY

This is a submission of data for Doxazosin mesilate in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

The majority of Marketing Authorisation licences are national licences, with two being Mutual Recognition Procedure (MRP)/Decentralised Procedure (DCP) licences for treatment of hypertension in adults, being used alone or in combination as well as for treatment of clinical symptoms in benign prostatic hyperplasia (BPH) and for reduced urinary flow associated with BPH in adults.

The MAH submitted information on a Japanese post-marketing study (DAZ-JP-90-301) which was open for enrolment to patients aged 16 years and older.

The rapporteur considers that the results from this non interventional study do not merit reflection in the product information.

MAH confirms there is no recommendation for a hypertension indication in the paediatric population and proposes to amend and align the existing text in the SmPC Section 4.2 and Package Leaflet Section 2 with current guidelines.

One MS commented and agreed with the Rapporteur. There have been no issues to be raised to the MAH at D89.
The WS procedure is therefore concluded with the below listed recommendation.

SmPC and PL changes are proposed in sections 4.2 of the SmPC and Section 2 of Package Leaflet.

Summary of outcome

☐ No change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: section 4.2

Section 4.2 Paediatric population:
'The safety and efficacy of Doxazosin mesilate [tradename] in children and adolescents have not been established.'

Paediatric information clarified in the accompanying current Package Leaflet (PL), Section 2:

'Before you take Doxazosin mesilate [tradename]
Doxazosin mesilate [tradename] is not recommended for use in children or adolescents below 18 years as safety and efficacy have not yet been established.'

☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

The MAH proposal to update the SmPC and PL in line with the current SmPC guideline is supported.

Section 4.2 Paediatric population:
'The safety and efficacy of Doxazosin mesilate [tradename] in children and adolescents have not been established.'

Paediatric information clarified in the accompanying current Package Leaflet (PL),
Section 2: 'Before you take Doxazosin mesilate [tradename]
Doxazosin mesilate [tradename] is not recommended for use in children or adolescents below 18 years as safety and efficacy have not yet been established.'

III. INTRODUCTION

The MAH submitted one completed non-interventional post marketing study for doxazosin mesilate including paediatric patients (age 16 and above), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

Doxazosin is selective alpha 1 adrenergic receptor inhibitor (post-junctional). Studies have shown that doxazosin competitively antagonizes the pressor effect of norepinephrine. The antihypertensive effect of doxazosin results from a decrease in systemic vascular resistance.

Doxazosin is also approved for the treatment of clinical symptoms in benign prostatic hyperplasia (BPH) and for reduced urinary flow associated with BPH in adults.

The submitted post marketing study was conducted from April 1990 to January 1996 for the purpose of the Japanese renewal in 1996 and designed to evaluate safety and usefulness of doxazosin for hypertension in Japanese adult patients. Paediatric use in this study was defined as use in patients younger than 15 years old.
The MAH confirmed that no subjects younger than 15 years old were enrolled. It was also stated by the MAH that a breakdown of demographics to indicate whether any patients aged 16 to less than 18 years were enrolled is not available. All available data are in Japanese and only available in hard paper copies filed in Japan.
Results from this study were not published and no other study data are available except for cases of serious adverse events (SAEs) recorded in the MAH safety database. The MAH confirmed as part of the submitted documents that no SAEs reported from this study were in subjects < 18 years old.

A short critical expert overview has also been provided.

The MAH stated that the submitted study does not influence the benefit:risk for doxazosin mesilate and that there is no consequential regulatory action needed. But it is proposed by the MAH to use the Art 45 procedure to update and align Section 4.2 and the PL according to current guidelines.

Rapporteur's comment:
The rapporteur notes that alpha blockade with doxazosin used off label is an essential part of pre-operative guideline recommendations for children with phaeochromocytoma to control malignant hypertension (i.e. Paediatric Endocrine Tumours - A Multi-Disciplinary Consensus Statement of Best Practice edited by Helen A Spoudeas and published 2005).
Additionally in clinical practice doxazosin is not only used for treatment of hypertension, but for a variety of indications in which α1 antagonistic effects provide a treatment rational, such as for treatment of dysfunctional voiding (El-Hefnawy AS et al, Urology. 2012) or for medical treatment of paediatric patients with distal ureteral stones (Erturhan S et al, Urology 2013).
The off label use of doxazosin is acknowledged by the fact that the British National Formulary for children (BNF-C) (2013/2014) provides dosing recommendations for doxazosin for the indication of hypertension and dysfunctional voiding.
The MAH did not provide data or any paediatric sponsored studies conducted with regards to the above mentioned paediatric uses of doxazosin (phaeochromocytoma and dysfunctional voiding) as part of this Paediatric Work-sharing procedure under Article 45.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study

Doxazosin mesilate 0.5mg, 1mg, 2mg and 4mg tablets were used in the submitted study.

IV.2 Non-clinical aspects

The MAH has not identified in-house non-clinical data with specific relevance to the use of doxazosin in patients younger than 18 years old.

IV.3 Clinical aspects

1. Introduction

The MAH submitted a translated study outline of study DAZ-JP-90-301.
No detailed study results were provided, as according to the MAH, the study was never intended for any other submission than for regulatory purposes in Japan and hence was never translated into English.

According to Japanese regulations at time of study conduct, patients were assigned to the following groups: Group a) ≤ 15 years – children; Group b) ≤ 64 years – adults; and Group c) ≥ 65 years - elderly. Therefore no paediatric patient has been included.
The MAH confirmed that study DAZ-JP-90-301 was never intended to support use of doxazosin in paediatric patients.

2. Clinical study

DAZ-JP-90-301 – a non-interventional post marketing study

- **Description of study outline**

DAZ-JP-90-301 was a non-interventional post marketing study conducted between April 1990 and January 1996 to evaluate safety and efficacy of doxazosin mesilate tablets for hypertension in the Japanese population age 16 and older.

The following information additional on the study outline has been provided by the MAH:

1. Target Disease:

Hypertension and hypertension due to phaeochromocytoma.

2. Exclusion Criteria:
   Patients with a history of hypersensitivity to this product.

3. Dosage and Administration:
   For adults, usually the therapy should be initiated with 0.5 mg once daily, and in case a satisfactory control of blood pressure is not achieved at this dose, the dosage should be gradually increased to 1-4 mg once a day orally at 1-2 week intervals. The dose should be adjusted appropriately according to the patient's age and symptoms but the highest daily dose should be 8 mg. For hypertension due to pheochromocytoma, however, the dose may be increased up to 16 mg a day.

4. Administration Period:
   As a general rule, administration period should be 4 weeks or longer.

5. Concomitant Drug:
   If any other drug is used during the therapy with this product, the name of drug, dose level, and administration period should be described.

6. Observation Period:
   (1) Blood pressure and number of pulses measurements
   Blood pressure and number of pulses measurements in sitting position or decubitus position if necessary should be conducted at every visit throughout the therapy with this drug.

   (2) Determination of hypertension severity:
   Severity of hypertension should be determined by the stage classification based on WHO standard or standard by Tokyo University No. 3 internal medicine (1984) at the start of therapy with this product.

   (3) For adverse reactions developed during the therapy with this product, the detailed information such as symptom, date of onset, degree of the symptom, clinical course, causality with the product and outcome should be recorded.

   (4) Laboratory tests should be conducted at the start of therapy with this product, during the therapy and after the therapy as much as possible. If any abnormalities are observed, changes (in laboratory values and causality with this product), progress, treatment, outcome of the variable, etc. should be recorded in detail.

7. Efficacy Evaluation Criteria:
   (1) Antihypertensive effect

   (2) Improvement degree of subjective symptoms

   (3) Overall safety rate

   (4) Usefulness

8. Other Information:
   (1) Withdrawal and discontinuation of administration
   In the case of discontinuation of administration of this product during the therapy due to reasons, indicate the timing, the reason of discontinuation, etc.

(2) In case if any serious or intractable adverse reactions which may be attributed to the drug are observed during the therapy, please contact our MR in a prompt manner.

(3) For precautions for the use of this product, please refer to the labeling.

➢ **Results**

The following results were submitted by the MAH:

A total of 10,340 subjects entered the study, 9436 completed and 906 patients discontinued. No patient 15 years or younger was enrolled. A breakdown of patients enrolled aged 16 to less than 18 years is not available to the MAH at present.
It was confirmed that more detailed information on patient demographics are generally accessible; however hard copy data source documents only available in Japanese would need to be re-analysed.

- Safety results

The MAH confirmed that no SAEs reported from this study were seen in patients younger than 18 years old.

3. Discussion on clinical aspects and conclusion

The MAH points out that Periodic Safety Update Reports (PSURs) have been routinely provided for doxazosin. No safety signals have been identified for the paediatric population from routine pharmacovigilance, and no changes relevant to paediatric use of doxazosin have been made to the MAH Core Data Sheet.
It is confirmed by the MAH that the most recent PSUR covered the period 01 January 2008 to 17 December 2010. Five cases involving doxazosin exposure in children were reported. Four cases reported no adverse events and one case reported a growth hormone deficiency that resolved with no treatment. This event had a temporal correlation with treatment with multiple antihypertensive drugs, including doxazosin.
The next scheduled PSUR will cover the period 18 December 2010 to 17 December 2015.

To support the doxazosin Risk Management Plan, the MAH conducted a cumulative search of the safety database for the period of 18 December 1986 (international birth date/ IBD) through 30 November 2013 to identify cases for patients younger than 18 years of age. A total of 47 cases reporting 92 adverse events (AEs) were identified.

During the period of 01 December 2013 through 15 May 2014, 3 cases (1 serious) reporting 2 adverse events in patients <18 years old were identified; all 3 cases were reports of accidental drug exposure.

Nine of the paediatric cases reported cumulatively from 18 December 1986 through 15 May 2014 indicated that doxazosin was administered for an indication of secondary hypertension or essential hypertension. Concurrent diagnoses or conditions were mentioned in a 17-year old with chronic renal failure, a 5-year-old with renovascular hypertension with a pathological diagnosis of fibromuscular dysplasia. It included a 15-year-old with prior bone marrow transplant and a 6-year-old receiving concurrent nicardipine, nitroglycerine and prednisolone. A 14-year-old with coarctation of the aorta, a 13-year-old with pheochromocytoma, a 12-year old with a prior heart transplant who was also receiving carbamazepine, tacrolimus, and mesuximide, a 17-year-old with Moyamoya disease, and a 9-year-old with diabetes and asthma.

The MAH concludes that the type and seriousness of adverse events recorded in the paediatric cases identified in the safety database did not indicate overt differences in doxazosin's safety profile between in adults and children.

Rapporteur's comments:
The submitted study under Article 45 has been a post-marketing study conducted in Japan in the 1990's including patients from the age of 16 years.
The rapporteur considers that due to the limitations of the study design (non-interventional study including adolescents older than 16 years amongst the adult cohort), it would not be possible to reach any robust efficacy conclusions concerning patients aged 16 to less than 18 years that would not merit reflection in the SmPC. Review of the study results has mainly a focus on safety aspects for paediatric patients aged 16 and above.
The exact number of paediatric patients enrolled (less than 18 years), as well as any detailed study results remain unavailable to the MAH despite best efforts to obtain them. After lengthy discussions between the rapporteur and the MAH, it was determined that it would not be feasible to obtain and translate the original Japanese paper-based dataset to identify the paediatric patients included in the study. Furthermore it is noted that due to the study design, the paediatric patients have been included and analysed within the adult study cohort, allowing very limited conclusions to be drawn from this study, with regards to the drug's safety and efficacy in patients less than 18 years of age. The rapporteur acknowledges the current evidence on doxazosin's off label use including the dosing recommendations in BNF-C as well as inclusion of doxazosin in treatment guidelines (such as for paediatric patients with phaeochromocytoma). However it is concluded that any paediatric data from the Japanese dataset would not add any valuable information to the currently licensed SmPC due to the limited paediatric population (i.e. adolescents older than 16 years) and the study design.
With regard to the safety profile and as described by the MAH, all safety data concerning paediatric patients have been analysed as part of the regular PSURs submissions. The last PSUR covered the period of January 2008 to December 2010 and overall the rapporteur concludes that there were no safety signals identified for the paediatric population.
Overall the rapporteur supports the MAH's conclusion that the submitted evidence does not influence paediatric use of doxazosin for the indication of treatment of hypertension.

The MAH's proposal to use this work-sharing procedure to update the SmPC wording in Section 4.2 and PL wording is supported by the rapporteur.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

One MS commented and agreed with the Rapporteur.
The submitted study does not provide any robust evidence that would influence current evidence on paediatric use of Doxazosin mesilate for the indication of treatment of hypertension.

- **Recommendation**

Type IB variation to be requested from the MAH by 20 March 2015.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance(s)
PFIZER	Cardura "PFIZER"	1 mg, 2 mg, 4 mg, 8 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Cardular 1mg "PFIZER"	1 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Cardular Uro 1mg "PFIZER"	1 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Supressin "PFIZER"	2 mg, 4 mg, 8 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Prostadilat "PFIZER"	2 mg, 4 mg, 8 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Cardular 2mg "PFIZER"	2 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Cardular Uro 2mg "PFIZER"	2 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Normothen "PFIZER"	2 mg, 4 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Benur "PFIZER"	2 mg, 4 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Carduran 2mg Comprimidos "PFIZER"	2 mg	Tablet, Uncoated, Oral	doxazosin mesilate
LABORATORIOS ALMIRALL, S.A.	PROGANDOL 2 mg Comprimidos	2 mg per unit	Tablet	DOXAZOSIN
PFIZER	Cardura XL "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardura XL 4mg "PFIZER"	4 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Carduran Retard "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Zoxan LP "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardular PP 4mg "PFIZER"	4 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardular 4mg "PFIZER"	4 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Cardular Uro 4mg "PFIZER"	4 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Cardular PP Uro 4mg "PFIZER"	4 mg	Tablet, GITS, Oral	doxazosin mesilate

PFIZER	Cardura Uro "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Benur XL "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardura 4mg "PFIZER"	4 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Carduran CR "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardura GITS "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardura XL 4 mg Prolonged-Release Tablets "PFIZER"	4 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Carduran Neo 4 mg comprimidos de liberacion modificada "PFIZER"	4 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Doxazosina Neo Pfizer 4 mg comprimidos de liberación modificada EFG "PFIZER"	4 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Carduran 4mg Comprimidos "PFIZER"	4 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Alfadil "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Alfadil BPH "PFIZER"	4 mg, 8 mg	Tablet, GITS, Oral	doxazosin mesilate
LABORATORIOS ALMIRALL, S.A.	PROGANDOL 4 mg Comprimidos	4 mg per unit	Tablet	DOXAZOSIN
LABORATORIOS ALMIRALL, S.A.	PROGANDOL NEO 4 mg Comprimidos de liberación modificada	4 mg per unit	Modified-release tablet	DOXAZOSIN
PFIZER	Cardura XL 8mg "PFIZER"	8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardular PP 8mg "PFIZER"	8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardular 8mg "PFIZER"	8 mg	Tablet, Uncoated, Oral	doxazosin mesilate
PFIZER	Cardular PP Uro 8mg "PFIZER"	8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Cardura XL 8 mg Prolonged-Release Tablets "PFIZER"	8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Carduran Neo 8 mg comprimidos de liberacion modificada "PFIZER"	8 mg	Tablet, GITS, Oral	doxazosin mesilate
PFIZER	Doxazosina Neo Pfizer 8 mg comprimidos de liberación modificada EFG "PFIZER"	8 mg	Tablet, GITS, Oral	doxazosin mesilate
LABORATORIOS ALMIRALL, S.A.	PROGANDOL NEO 8 mg Comprimidos de liberación modificada	8 mg per unit	Modified-release tablet	DOXAZOSIN