LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Urozosin
5 mg and 10 mg, prolonged release tablets
(Alfuzosin hydrochloride)

SE/H/463/01-02/E01

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This module reflects the scientific discussion for the approval of Urozosin 5 mg and 10 mg prolonged release tablets. The procedure was finalised at 2008-02-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Hexal AG has applied for a marketing authorisation for Urozosin 5 mg and 10 mg prolonged release tablets claiming essential similarity to Xatral prolonged-release tablets 5 mg and Xatral OD prolonged-release tablets 10 mg marketed in Sweden by Sanofi-Synthelabo. The product contains alfuzosin hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference products used in the bio-equivalence studies are UroXatralS 5 mg marketed by Sanofi-Synthelabo in Germany and Xatral LP 10 mg marketed by Sanofi-Synthelabo in France.

II. QUALITY ASPECTS

II.1 Introduction

Urozosin is presented in the form of prolonged release tablets containing 5 mg respective 10 mg of alfuzosin hydrochloride. The excipients are lactose monohydrate, hypromellose, povidone, and magnesium stearate. The tablets are packed in PVC/PVDC/aluminium blisters.

II.2 Drug Substance

Alfuzosin hydrochloride has a monograph in the Ph Eur. and the manufacturer holds a CoS of the monograph. Alfuzosin hydrochloride is a white, crystalline powder which is freely soluble in water, sparingly soluble in alcohol and practically insoluble in methylene chloride. The structure of alfuzosin hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on 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 data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Urozosin 5 mg and 10 mg prolonged release tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

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 data presented support the shelf life claimed in the SPC, with no special storage precautions for Urozosin 5 mg prolonged release tablets and with storage conditions , do not store above 30°C, for Urozosin 10 mg prolonged release tablets.

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 such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

5 mg tablet:

One randomized 2-way crossover bioequivalence study with Alfuzosin 5 mg prolonged-release tablet (Cimex Development, Switzerland) and UroXatral S 5 mg (Sanofi-Synthelabo, Germany) was submitted. Each study period consisted of three phases: single dose phase, multiple dose phase and food effect phase. The primary study parameters were C_{max}, C_{min} and AUC on day 7 (fasting). C_{max} and AUC on day 8 were used for investigating food effect and C_{max} and AUC on day 1 was used for descriptive purposes only.

10 mg tablet:

One randomized 2-way crossover bioequivalence study in the fed state with Alfuzosin 10 mg prolonged-release tablets (Cimex Development, Switzerland) and Xatral LP 10 mg (Sanofi-Synthelabo, France) was submitted to investigate the bioequivalence after single dose and after multiple dosing. The primary study parameters in this study were C_{max}, C_{min} and AUC on day 7, to establish bioequivalence in the fed state. Secondary parameters were the single dose parameters from day 1. An additional randomized single dose 2-way crossover bioequivalence study in the fasted state was also submitted.

The results of the studies are presented below.

5 mg tablet:

Multiple dose, fasting condition 5 mg:

The results are given in the following table as geometric mean (CV%).

Preparation	**C_{max} (ng/ml)**	**C_{min} (ng/ml)**	**t_{max} (h)**	**AUC_{τ} (ng*h/ml)**
Test	17.0 (33%)	7.9	5.2	149.6 (33%)
Reference	17.2 (28 %)	7.5	3.2	140.5 (30%)
Ratio	0.99	1.05		1.07
90% CI	*0.91-1.08*	*0.93-1.18*		*0.96-1.18*

Single dose, fasting conditions 5 mg:

The results are given in the following table as geometric mean (CV%).

Preparation	**C_{max} (ng/ml)**	**t_{max} (h)**	**$AUC_{0-\infty}$ (ng*h/ml)**
Test	8.7 (34%)	5.5	94 (36%)
Reference	7.8 (31%)	5.2	95 (33%)
Ratio	1.11		0.99
90% CI	*1.02-1.22*		*0.88-1.12*

Food effect 5 mg:

The results are given in the following table as geometric mean (CV%).

Condition tested	**C_{max} (ng/ml)**	**C_{min} (ng/ml)**	**t_{max} (h)**	**AUC_{τ} (ng*h/ml)**
Fed	17.6 (34%)	8.8	5.0	147.3 (28%)
Fasted	17.1	7.7	5.2	145.0
Ratio	1.03	1.14		0.97
90% CI	*0.96-1.10*	*1.06-1.25*		*0.90-1.05*

10 mg tablet:

Multiple dose, fed condition 10 mg:

The results are given in the following table as geometric mean (CV%).

Preparation	**C_{max} (ng/ml)**	**C_{min} (ng/ml)**	**t_{max} (h)**	**AUC_{τ} (ng*h/ml)**
Test	10.6 (32%)	3.2 (60%)	5.9	144 (38%)
Reference	10.7 (24%)	3.3 (62%)	6.7	152
Ratio	0.99	0.96		0.95
90% CI	*0.94-1.05*	*0.84-1.10*		*0.89-1.02*

Single dose, fed conditions 10 mg:

The results are given in the following table as geometric mean (CV%).

Preparation	**C_{max} (ng/ml)**	**t_{max} (h)**	**$AUC_{0-\infty}$ (ng*h/ml)**
Test	7.7 (38%)	6.7	104.1 (48%)
Reference	7.9 (36%)	7.4	116.4 (48%)
Ratio	0.98		0.90
90% CI	*0.92-1.04*		*0.82-0.98*

Single dose, fasting conditions 10 mg:

The results are given in the following table as geometric mean (CV%). (n=35)

Preparation	C_{max} (ng/ml)	t_{max} (h)	AUC_{0-t} (ng*h/ml)	$AUC_{0-\infty}$ (ng*h/ml)
Test	7.22 (51.6)	3.67 (1-8)	99.22 (50.1)	113.57 (50.3)
Reference	7.78 (55.4)	4.45 (2-10)	108.66 (46.9)	122.67 (44.0)
Ratio	0.94	-	0.91	0.93
90% CI	0.84-1.04*		0.80-1.05*	0.81-1.06*

*Parametric confidence intervals.

Bioequivalence, using the standard acceptance range 80-125% for C_{max} and AUC, was demonstrated. No effect of food on was detected.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refers to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed, but an acceptable bridging to a test for a similar product has been made.

The risk/benefit ratio is considered positive and Urozosin 5 mg and 10 mg prolonged release tablets are recommended for approval.

VI. APPROVAL

The 1st wave Repeat Use Procedure for Urozosin 5 mg and 10 mg prolonged release tablets was successfully finalised on 2008-02-20.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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