Public Assessment Report

Scientific discussion

Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets

(alfuzosin hydrochloride)

NL/H/3015/001/MR

Date: 9 September 2014

This module reflects the scientific discussion for the approval of Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets. The procedure was finalised on 6 March 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 10-12.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets from Aurobindo Pharma B.V.

The product is indicated for treatment of moderate to severe functional symptoms of benign prostatic hyperplasia (BPH).

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Xatral® XR 10 mg prolonged-release tablets (NL License RVG 23923) which has been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 4 October 1999 (original product).

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Cyprus, Czech Republic, Germany, Ireland, Malta, Romania, Spain and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Alfuzosine HCl Aurobindo 10 mg is a white to off-white round, biconvex, film-coated tablet debossed with 'X' on one side and '47' on the other side.

The prolonged-release tablets are packed in PA/Aluminium/PVC/Aluminium blister packs and white opaque, round HDPE bottles containing silica gel sachets.

The excipients are:
Tablet core – hypromellose, hydrogenated vegetable oil, povidone, anhydrous calcium hydrogen phosphate, carbomer, colloidal anhydrous silica, magnesium stearate
Tablet coat - hypromellose, propylene glycol, titanium dioxide.

II.2 Drug Substance

The active substance is alfuzosin hydrochloride, an established active substance, described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline, slightly hygroscopic powder, which is freely soluble in water. Alfuzosin is known to exist in anhydrous-, mono-, di-, tri- and tetra hydrate forms and is manufactured as the anhydrous form. Alfuzosin has an asymmetric carbon leading to two enantiomers. The drug substance is manufactured as a racemic mixture.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP, with additional requirements for particle size, microbiological contamination and polymorphic form. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Except for a slight increase in water content, no changes or trends were observed during storage. The proposed retest period of 2 years without additional storage requirements is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies regarded the characterisation of the originator product, optimization of the tablet formulation and manufacturing process and the performance of comparative dissolution studies. The batch used in the bioequivalence studies is manufactured according to the finalized manufacturing process and drug product composition. Comparative dissolution studies with the test product versus the innovator were performed in different media. The UK and NL reference products were demonstrated to have similar dissolution profiles. Use of the UK product in the bioequivalence studies is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of sifting, blending, lubrication, compression and coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale and three full-scale batches.

Control of excipients
The excipients comply with the requirements of the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, water, average weight, dissolution, uniformity of dosage units, assay, related substances, thickness, microbial contamination and identification of titanium dioxide. Except for water content, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale and three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/Al-blisters and HDPE containers (of 30 and of 1000 tablets). No changes are observed at both storage conditions. The drug product was demonstrated to be photostable. The proposed shelf-life of 2 years without any special storage requirements is justified.
Stability data has been provided demonstrating that the product remains stable for 24 months following first opening, when stored in 1000 count HDPE containers at 25°C/60% RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Alfuzosine HCl Aurobindo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Alfuzosine HCl Aurobindo is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Xatral XR 10 mg, prolonged-release tablets which is available on the European market. Reference is made tot the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Alfuzosin is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Alfuzosine HCl Aurobindo 10 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Xatral XL 10 mg tablets (Sanofi-Synthelabo, UK). The two single-dose bioequivalence studies under fasting and fed conditions, and a multiple dose study to support this application are considered sufficient, adequate and in accordance with the guidelines, requiring such studies for prolonged-release tablets.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The analytical methods have been adequately validated and areconsidered acceptable for analysis of the plasma samples. The methods used for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – single-dose, fasted conditions

Design
An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-33 years. Each subject received a single dose (10 mg) of one of the 2 alfuzosin formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours after administration of the products.

Results
Three subjects dropped out: two because of vomiting and one because he did not check-in for period II.

Pharmacokinetic and statistical analyses were carried out on 33 subjects.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of alfuzosin under fasted conditions.

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	145 ± 64	149 ± 65	9.6 ± 3.8	5.0 (2.0 – 12.0)	6.5 ± 2.3
Reference	165 ± 94	170 ± 96	10.3 ± 6.2	5.0 (3.0 – 24.0)	6.5 ± 1.9
***Ratio (90% CI)**	0.91 (0.82-1.02)	0.92 (0.82-1.03)	0.98 (0.88-1.08)	--	--
CV (%)	27.8	27.8	26.1	--	--

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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of alfuzosin under fasted conditions, it can be concluded that Alfuzosine HCl Aurobindo and Xatral XL 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – single-dose, fed conditions

Design
An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 20-33 years.

Each subject received a single dose (10 mg) of one of the 2 alfuzosin formulations. The tablets were administered in solid form with 240 ml water 30 min after intake of a high caloric, high fat, standardized breakfast (85 g eggs fried in butter, 26 g mutton fry, 54 g bread slices with butter, 45 g fried potatoes and 240 ml milk (985 kcal (60% from fat, 25% from carbohydrates, 15% from proteins)). There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours after administration of the products.

Results
One subject dropped out: before dosing in period I, because of vomiting. Pharmacokinetic and statistical analyses were carried out on 35 subjects.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of alfuzosin under fed conditions.

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	137 ± 49	141 ± 50	10.2 ± 3.8	6.0 (3.0 – 16.0)	6.5 ± 2.0
Reference	145 ± 64	149 ± 65	11.6 ± 6.4	7.0 (1.0 – 14.0)	6.4 ± 2.2
***Ratio (90% CI)**	0.97 (0.88-1.07)	0.97 (0.88-1.08)	0.94 (0.85-1.04)	--	--

CV (%)	25.0	25.0	26.0	--	--

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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of alfuzosin under fed conditions, it can be concluded that Alfuzosine HCl Aurobindo and Xatral XL 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study III – multiple-dose, fed conditions

Design
An open label, multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover, steady-state bioequivalence study was carried out under fed conditions in 38 healthy male subjects, aged 20-34 years.
Each subject received the test and reference alfuzosin prolonged-release formulations once daily for seven consecutive days a single dose (10 mg). The tablets were administered in solid form with 240 ml water 30 min after intake of a non high fat, standardized breakfast (650 kcal (30% from fat)). For each subject there were 2 dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose at day 1-6 and at day 7 at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20 and 24 hours after administration of the products

Results
Two subjects voluntarily withdrew in period I and II. Pharmacokinetic and statistical analyses were carried out on 36 subjects.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=36	**AUC_{τ}** ng/ml/h	**$C_{max,ss}$** ng/ml	**$C_{min,ss}$** ng/ml	**PTF%** %
Test	196 ± 73	16.2 ± 7.7	3.3 ± 1.4	153 ± 36
Reference	212 ± 96	16.2 ± 8.6	3.4 ± 1.5	141 ± 39
***Ratio (90% CI)**	0.94 (0.88-1.01)	1.01 (0.93-1.10)	0.98 (0.90-1.08)	--
CV (%)	17.9	21.3	23.2	--

AUC_{τ} area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

The 90% confidence intervals calculated for AUC_{τ}, $C_{max,ss}$ and $C_{min,ss}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of alfuzosin at steady state, it can be concluded that Alfuzosine HCl Aurobindo and Xatral XL 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence studies have 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Alfuzosine HCl Aurobindo.

Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity - Patients with Previous history of orthostatic hypotension - Hepatic insufficiency - Combination with other alpha 1 receptor blockers/ or dopamine receptor agonists - Patients with antihypertensives treatments or nitrates - Patients with acute cardiac failure - Patients with congenital QTc prolongation, with a known history of acquired QTc prolongation or who are taking drugs known to increase the QTc interval *Alfuzosin HCl Aurobindo 2.5 mg film-coated tablets:* - Patients suffering from incontinence due to overflow, anuria or prolonged renal insufficiency - Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
Important potential risks	- Myocardial infarction - Athralgia - Vomiting and increased blood glucose levels in diabetic patients - Interoperative Floppy Iris Syndrome (IFIS)
Missing information	- Use in patients with severe renal function disorder (creatinine clearance < 30 ml/min

The member states agree that no additional pharmacovigilance activities beyond routine measures are required.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xatral® XR 10 mg prolonged-release tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is

similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. A total of 23 participants were questioned. The initial testing involved 3 participants to identify any major changes needed to the PL. Thereafter, two rounds of testing were conducted with 10 participants. The results have shown that the information most relevant to the patient can be found and understood in a good way. The package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Xatral XR 10 mg prolonged-release tablets. Xatral is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents under fasted and fed condition, and at steady state.

The Board followed the advice of the assessors. Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets was authorised in the Netherlands on 9 January 2012.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, recognized the assessment of the MEB, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 6 March 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

Summary Public Assessment Report

Generics

Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets

(alfuzosine hydrochloride)

NL/H/3015/001/MR

Date: 9 September 2014

Summary Public Assessment Report

Generics

Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets
Active substance: alfuzosine hydrochloride

This is a summary of the public assessment report (PAR) for Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Alfuzosine HCl Aurobindo.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Alfuzosine HCl Aurobindo and what is it used for?
Alfuzosine HCl Aurobindo 10 mg is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Xatral XR 10 mg, prolonged-release tablets.

This medicine is used to treat moderate to severe symptoms of Benign Prostate Hyperplasia. This is a condition where the prostate gland enlarges (hyperplasia), but the growth in itself is not cancerous (benign). It occurs most often in older men.

How is this medicine used?
The medicine can only be obtained with a prescription. The usual dose is one Alfuzosine HCl Aurobindo 10 mg prolonged release tablet once a day. It does not need to be adjusted for elderly (over 65 years). The tablet should be swallowed whole with plenty of fluid and must be taken after a meal.

How does this medicine work?
The prostate gland is situated under the bladder surrounding the urethra (the tube that takes your urine to the outside of the body). With age, the muscular prostate gland may grow and press the urethra making it narrower. This may cause problems with urination such as frequent urination and difficulty in passing urine. Alfuzosine HCl Aurobindo works by relaxing the prostate gland muscle. This reduces the narrowing of the urethra and so makes it easier to pass urine.

How has this medicine been studied?
Because Alfuzosine HCl Aurobindo is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Xatral XR 10 mg. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of this medicine?
Because it is a generic medicine and is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as the reference medicine.

What are the benefits and possible side effects of this medicine?
Because Alfuzosine HCl Aurobindo is a generic medicine and is bioequivalent to the reference medicine Xatral XR, its benefits and possible side effects are taken as being the same as the reference medicine.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, Alfuzosine HCl Aurobindo 10 mg has been shown to have comparable quality and to be bioequivalent to Xatral XR. Therefore, the view was that, as for this reference medicine, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Alfuzosine HCl Aurobindo, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about this medicine
In the Netherlands, the marketing authorisation for Alfuzosine HCl Aurobindo 10 mg, prolonged-release tablets was granted on 9 January 2012.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human. For more information about treatment with Alfuzosine HCl Aurobindo, read the package leaflet (http://mri.medagencies.org/download/NL_H_3015_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in September 2014.