CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Alfuzosine HCl Aurobindo 2.5 mg, film-coated tablets
Aurobindo Pharma B.V., the Netherlands

alfuzosin (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2311/001/MR
Registration number in the Netherlands: RVG 103826

31 October 2011

Pharmacotherapeutic group:	alpha-adrenoreceptor antagonists
ATC code:	G04CA01
Route of administration:	oral
Therapeutic indication:	moderate to severe functional symptoms of benign prostatic hyperplasia (BPH)
Prescription status:	prescription only
Date of first authorisation in NL:	21 October 2010
Concerned Member States:	Mutual recognition procedure with UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

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 2.5 mg, film-coated tablets from Aurobindo Pharma B.V. The date of authorisation was on 21 October 2010 in the Netherlands.

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 SPC.

Alfuzosin, a racemic compound, is an orally active quinazoline derivative that selectively blocks postsynaptic alpha-1-receptors. In vitro studies have shown that the substance acts selectively on alpha-1-receptors in the trigone of the urine bladder, the urethra and the prostate gland. The clinical symptoms of benign prostate hyperplasia are not only related to the size of the prostate but also to the sympathicomimetic nerve impulses which through stimulation of the postsynaptic alpha-receptors increase the tension of the smooth muscles of the lower urinary tract. Through treatment with alfuzosin the smooth muscles relax as a result of which the urine flow improves.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Xatral 2.5 mg film-coated tablets (NL License RVG 13689) which has been registered in the Netherlands by Sanofi-aventis since 13 June 1990. In addition, reference is made to Xatral authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Xatral 2.5 mg film-coated tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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 sparingly soluble in water and in alcohol, practically insoluble in methylene chloride. Alfuzosin hydrochloride is known to exist in anhydrous-, mono-, di-, tri- and tetra hydrate forms and is manufactured as the anhydrous form.

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 new 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 Ph.Eur. and the CEP, with additional requirements for impurities, polymorphic form, residual solvents, particle size and microbial limits. 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 three 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 at 40°C/75%RH (6 months). The batches were adequately stored. Based on the results provided, a retest period of 2 years in the proposed packaging materials has been granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Alfuzosine HCl Aurobindo 2.5 mg is a white to off-white round, biconvex, film-coated tablet debossed with ‘X’ on one side and ‘31’ on the other side.

The film-coated tablets are packed in PVC/PVdC-Aluminium foil blister packs or (HDPE) bottle packs with polypropylene closure.

The excipients are:
Tablet core - sodium starch glycolate (Type A)Cellulose microcrystalline, lactose monohydrate, povidone, magnesium stearate
Tablet coat - hypromellose, macrogol 400, titanium dioxide (E171).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the innovator product, optimization of excipient concentrations and comparative dissolution studies with the innovator product. The comparative dissolution studies were performed in different media. The results demonstrate that the dissolution profiles of the test and reference batch are similar in the tested dissolution media.
The batch used for the bioequivalence studies is manufactured according to the finalized formulation and manufacturing process. The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process consists of compounding, dry mixing, wet granulation, milling, final blending, 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 batches. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorization.

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, identification, water content, average weight, dissolution, uniformity of dosage units, assay, related substances, thickness, identification of titanium dioxide and microbial contamination. Except for water content, assay and related substances, the release and shelf-life requirements are identical. The proposed 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 batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided 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 PVC-PVdC/Al-blisters or HDPE bottles (of 100 and 1000 tablets). All parameters remained within the specified limits. Photostability results from forced degradation studies show almost no degradation for alfuzosin hydrochloride. Results have been provided that no additional storage requirements are needed. The proposed shelf life of 2 years without additional storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose monohydrate, no excipients are used of human or animal origin. Lactose monohydrate is derived from the milk of healthy animals and no other ruminant materials are used. For the other excipients BSE statements are provided. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Xatral 2.5 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of alfuzosin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Alfuzosin is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Alfuzosine HCl Aurobindo 2.5 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Xatral 2.5 mg tablets (Sanofi-Synthelabo, France), marketed in the UK.

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

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 18-33 years. Each subject received a single dose (2.5 mg) of one of the 2 alfuzosine formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hrs after dosing. There were 2 dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20 and 24 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject did not report for Period II. Thirty-five subjects completed the study entirely and were included in the pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of alfuzosin under fasted 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	55.4 ± 27.9	59.6 ± 29.6	7.51 ± 4.77	1.50 ± 1.27	6.4 ± 2.0
Reference	55.6 ± 40.2	60.3 ± 43.9	7.66 ± 5.62	1.25 ± 1.33	6.6 ± 3.3
***Ratio (90% CI)**	1.07 (0.98-1.17)	1.06 (0.97-1.16)	1.02 (0.91-1.14)	--	--
CV (%)	21.5	21.7	27.3	--	--

$AUC_{0-\infty}$ 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 2.5 mg and Xatral 2.5 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.

Alfuzosin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of alfuzosin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has 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).

Risk management plan

Alfuzosin was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of alfuzosin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Xatral.

Readability test

The package leaflet has not been evaluated via a user consultation study. A bridging report was submitted in which reference is made to the PIL for Alfuzosine HCl Aurobindo 10 mg film-coated tablets. Mockups for both PILs have same layout and design (same in-house style), same font and same text colour. Moreover the Daughter PIL has the larger font size than the Parent PIL, which is more patient friendly. In both PIL mockups the headings are presented as white letters with black back ground which enhances findability. The critical safety sections (Contraindications & warnings) in both Parent and Daughter PIL are laid out in bullet points.
Overall, the layout of the sections and subsections in both leaflets is almost identical. The differences are negligible and not expected to influence readability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Alfuzosine HCl Aurobindo 2.5 mg, film-coated tablets has proven chemical-pharmaceutical quality and is a generic form of Xatral 2.5 mg film-coated 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.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is in the agreed templates and consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Alfuzosine HCl Aurobindo 2.5 mg, film-coated tablets was authorised in the Netherlands on 21 October 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Alfuzosine HCl Aurobindo 2.5 mg, film-coated tablets with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 4 August 2011.

The date for the first renewal will be: July 2016.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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