CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Alfuzosinehydrochloride 2,5 mg PCH, film-coated tablets Pharmachemie B.V., the Netherlands

Alfuzosine hydrochloride

This assessment report is published by the MEB following 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/1178/001/MR
Registration number in the Netherlands: RVG 31635

30 June 2009

Pharmacotherapeutic group:	alpha-adrenoreceptor antagonists.
ATC code:	G04C A01
Route of administration:	Oral
Therapeutic indication:	Treatment of the functional symptoms of benign prostatic hyperplasia (BPH).
Prescription status:	prescription only
Date of authorisation in NL:	1 March 2006
Concerned Member States:	DE, DK, ES, IT and 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 (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Alfuzosinehydrochloride 2,5 mg PCH, film-coated tablets, from Teva Pharma B.V., the Netherlands. The first date of authorisation was on 1 March 2006 in the Netherlands.

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

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

Alfuzosin is a selective alpha1-adrenoreceptor antagonist, bears structural similarity to prazosin, and both are quinazoline derivatives. Molecular weight: 426. Freely soluble in water, sparingly soluble in alcohol.
Alfuzosin is rapidly absorbed form the gastrointestinal tract in most patients (t_{max} 1.5-2 h, range 0.5-6h) with a bioavailability of ~65%. The presence of food does not significantly alter its absorption. Plasma protein binding of alfuzosin is ~90%, primarily to alpha-1-acid glycoprotein. Alfuzosin is extensively metabolised by CYP 3A followed by glucuronide or sulphate conjugation of metabolites. <11% of the dose is recovered unchanged in the urine. Plasma elimination half-life of oral alfuzosin ranges from 3 to 9 hours.

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

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 applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Xatral CR 10 mg prolonged release tablets, registered in Hungary. 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 preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to this product.

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 these product types 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.). The Ph.Eur. is the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Alfuzosin HCl is a white or almost white crystalline powder that can exist in several crystal forms. Crystals with 0, 1, 2, 3, and 4 water molecules are known. It is freely soluble in water, sparingly in alcohol, and practically insoluble in methylene chloride.

The active substance is supplied by one Active Substance Manufacturer (ASM). For the ASM the certificate of suitability (CEP) procedure is used. Under this official Certification Procedure of the European Directorate for the Quality of Medicines (EDQM) of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a CEP 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 Ph.Eur.

Quality control of drug substance
The active substance specification adopted by the marketing authorisation holder (MAH) is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for residual solvents, microbiological purity, particle size and powder density. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 18 months when stored under the stated conditions.

Medicinal Product

Composition
Alfuzosinhydrochloride 2.5 mg PCH film-coated tablets are white, round, slightly arched tablets debossed “LFN” on one side and “2.5” on the other.

The excipients are: lactose monohydrate, povidone, sodium starch glycolate, cellulose (microcrystalline), magnesium stearate, hypromellose, titanium dioxide (E171), macrogol, glycerol triacetate.

The tablets are packed in transparent PVC – aluminium blisters.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. No unusual excipients are used. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs. The specifications adopted by

the MAH are considered adequate to control the quality of the excipients. A bioequivalence study has been performed in order to demonstrate equivalence versus the reference product Xatral.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for tablets in the Ph.Eur. and includes tests for, amongst others, identification, assay, dissolution rate, uniformity of dosage, determination of degradation products, and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of two pilot from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for two pilot batches stored at 25ºC/60%RH and 40ºC/75%RH in accordance with applicable European guidelines. On the basis of the data submitted, a shelf life of 2 years could be granted. Alfuzosine 2.5 mg PCH should be stored in the original packaging to protect from light. The MAH committed to submit the stability data of the first three commercial batches.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

Alfuzosine 2.5 mg PCH 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 hydrochloride is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Alfuzosine 2.5 mg PCH is compared with the pharmacokinetic profile of the reference product Xatral 2.5 mg 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 in different member states.

The test tablet used is from a pilot batch but with the same manufacturing process.

A randomised, open-label, single-dose, 2-way cross over, bioavailability study was carried out under fasting conditions in 32 healthy male subjects, aged 18-55 years. Each subject received after an overnight fast, a single dose (2.5 mg) of one of the alfuzosin formulations with 240 ml water. For each subject there

were 2 dosing periods, separated by a washout period of at least 7 days, which is sufficient for a compound with an estimated plasma elmination half-life of 3-9 hours. Blood samples were taken predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.83, 2.17, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours after administration of the alfuzosin tablets.
There was one drop-out, not related to medication, and pharmacokinetic parameters were evaluated of thirty-one subjects.

AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, C_{min}, t_{max} and $t_{1/2}$ were calculated according to standard procedures. Statistical evaluation of the data was performed on the log-transformed AUC_{0-t}, AUC_{inf}, and C_{max} values using BIOSTAT. For t_{max} the non-parametic confidence interval for the median difference is reported.

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) [n=31]

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	70 ± 27	76 ± 29	10 ± 4	1.0 (0.75-6)	6.1 ± 1.4
Reference	67 ± 26	72 ± 28	10 ± 4	1.0 (0.75–3)	6.3 ± 1.0
***Ratio (90% CI)**	1.05 (1.00-1.10)	1.05 (1.00-1.09)	1.04 (0.95-1.03)		
CV (%)	11%	11%	22%		

$AUC_{0-\infty}$ 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 AUC0-t, AUC0-∞ and Cmax are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25.
The results demonstrate that test and reference tablets are bioequivalent following single dose administration, both under fasted or (high-fat) fed conditions. Moreover, at steady state under fed conditions, test and reference tablets were bioequivalent with regard to the rate and extent of absorption.

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).

Readability test
The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The qualitative method used. Twenty three male subjects all educated (school or further education) were enrolled. Age distribution: 5 (22%) participants were in the category 41-65 years, and 18 (78%) participants were over 65 years. This is acceptable as alfusozine hydrochloride is indicated for men (>65 years) only. The questions were of good quality and cover the most important sections of the leaflet.

The readability test has been adequately performed. The test process involved two rounds in a sufficient number of participants.

Risk Management Plan

Alfusozin was first approved in 1987 in the EU, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of alfusozin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SmPC. 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.

PSUR cyclus and renewal date

An European harmonised birth date has been allocated (12 November 1987) and subsequently the first data lock point for Alfuzosin is January 2010. The 1st PSUR will cover the period from March 2006 until November 2009. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal is agreed to be 7 March 2013.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Alfuzosine 2.5 mg PCH has a proven chemical-pharmaceutical quality and is a generic form of Xatral 2.5 mg film-coated tablets. Xatral 2.5 mg film-coated tablets are a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the European guidance documents. The SmPC is consistent with that of the reference product.

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

The SmPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Alfuzosinehydrochloride 2.5 mg PCH was authorised in the Netherlands on 1 March 2006.

There was no discussion in the CMD(h). Agreement between the concerned member states was reached during a written procedure. The mutual recognition procedure was finished on 7 March 2008. The concerned member states, on the basis of the data submitted, considered that Teva Pharma B.V. (the Netherlands) has demonstrated bioequivalence for Alfuzosine 2.5 mg PCH prolonged release tablets with the reference product and have therefore granted a marketing authorisation.

The following post-approval commitments have been made during the procedure:

Quality – Medicinal product

- The MAH committed to submit the stability data of the first three commercial batches.

List of abbreviations

ASMF	Active Substance Master File
ASMs	Active Substance Manufacturers
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
JP	Japanese Pharmacopoeia
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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	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
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/1178 /001/IA/00 1	IA	9-7-2008	23-7-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/1178 /001/IA/00 2	IA	9-7-2008	23-7-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/1178 /001/IA/00 3	IA	9-7-2008	23-7-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/1178 /001/IA/00 4	IA	17-7-2008	31-7-2008	Approval	N