CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Alfuzosine HCl Ranbaxy 10 mg, prolonged release tablets Ranbaxy Belgium N.V., Belgium

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/1327/001/MR
Registration number in the Netherlands: RVG 32989

14 August 2008

Pharmacotherapeutic group:	alpha-adrenoreceptor antagonists.
ATC code:	G04C A01
Route of administration:	Oral
Therapeutic indication:	Treatment of moderate to severe functional symptoms of benign prostate hyperplasia (BPH).
Prescription status:	prescription only
Date of authorisation in NL:	17-10-2007
Concerned Member States:	Mutual recognition procedure with DK, EL, FR, IE, IS, IT, NO, PL, PT, SE, 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 (SPC), 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 Alfuzosine HCl Ranbaxy 10 mg, prolonged release tablets, Ranbaxy Belgium N.V., Belgium. The first date of authorisation was on 17 October 2007 in the Netherlands.

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

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

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 10 mg XR, which has been registered in the Netherlands (NL License RVG 23923) by Sanofi-Aventis since 4 October 1999. In addition, reference is made to Xatral 10 mg XR prolonged release tablets authorisations in the individual Member States (reference product). As Xatral 2.5 mg (Sanofi-Aventis, the Netherlands; date of approval 13-06-1990) has been granted an initial marketing authorisation (article 6(1) of directive 2001/83/EC) for more then 10 years ago in the EEA, and Xatral 10 mg XR is an additional pharmaceutical form of the former, all these marketing authorisations shall be considered as belonging to the same global marketing authorisation in particular for the purpose of article 10(1).

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 three bioequivalence studies 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 Finland. 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.

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 and excipients
The active substance is alfuzosin hydrochloride, is 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 in water, sparingly in alcohol, practically insoluble in methylene chloride. 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. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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.

Stability data on the active substance have been provided for three production scaled batches for each supplier in accordance with applicable European guidelines demonstrating the stability of the active substance for 2 years when stored under the stated conditions.

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.

Medicinal Product

Composition
Alfuzosine HCl Ranbaxy 10 mg are white to off-white, round, uncoated, biconvex tablets with flattened edges, debossed with ‘RY 10’ on one side.

The excipients are: Lactose anhydrous, Colloidal anhydrous silica, Povidone, Talc, Magnesium stearate, Hypromellose, Hydroxypropyl cellulose.

The tablets are packed in 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. 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 product is produced by using non standard manufacturing techniques (not by the use of any specific type of equipment etc). Prolonged-release tablets are considered a critical dosage form. This means that the process must be validated at full production scale at the time of dossier submission.

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 mass, 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 from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for three production scaled batches in accordance with applicable European guidelines. No specific storage conditions need to be included in the SPC or on the label.

On the basis of the data submitted, a shelf life of 24 months could be granted.

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 HCl Ranbaxy 10 mg is a generic formulation of Xatral 10 mg XR 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 three bioequivalence studies in which the pharmacokinetic profile of the test product Alfuzosine HCl Ranbaxy 10 mg is compared with the pharmacokinetic profile of the reference product Xatral CR 10 mg prolonged release tablets. To prove bioequivalence, the applicant submitted a single dose BE study under fasted conditions, a single dose study under fed conditions, and a multiple dose bioequivalence study under fed conditions, table 1 to 3 respectively.

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.

Study 1

In this study a single dose of 10 mg was administered in a randomised two-way cross-over design under fasted conditions. The washout period between different periods was 14 days. Forty healthy, male volunteers, aged 19-60 years, were included in this study. There were three drop-outs, therefore data have been analysed from 37 volunteers (table1).

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) [n=37]

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	172.2 ± 78.6	181.6 ± 83.2	9.23 ± 3.23	5.3 ± 1.8 (3.0-10)	11.3 ± 6.4
Reference	164.4 ± 79.1	167.9 ± 78.6	8.87 ± 4.77	5.1 ± 2.0 (2.0-10)	10.0 ± 3.8
***Ratio (90% CI)**	1.07 (0.96-1.19)	1.08 (0..98-1.19)	1.09 (0.96-1.24)		
CV (%)	27.5 %	24.5 %	34.0 %		

$AUC_{0-\infty}$ 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*

Study 2

In this study a single dose of 10 mg was administered in a randomised two-way cross-over design under fed conditions. The washout period between different periods was 14 days. Thirty-two healthy, male volunteers, aged 18-51 years, were included in this study. There were four drop-outs, therefore data have been analysed from 28 volunteers (table 2).

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) [n=28].

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	232.9 ± 92.8	235.2 ± 93.6	15.5 ± 5.1	7.1 ± 2.0 (4.0-11)	8.6 ± 2.6
Reference	249.0 ± 124.7	251.1 ± 125.6	16.1 ± 8.3	7.8 ± 4.6 (2.0-24)	8.6 ± 2.3
***Ratio (90% CI)**	0.96 (0.87-1.06)	0.96 (0.88-1.06)	1.01 (0.90-1.13)		
CV (%)	21.4 %	21.0 %	25.6 %		

$AUC_{0-\infty}$ 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*

Study 3

In this study multiple doses of 10 mg were administered in a randomised two-way cross-over design under fed conditions. The washout period between different periods was 14 days. Thirty-two healthy, male volunteers, aged 18-51 years, were included in this study. There were two drop-outs, therefore data have been analysed from 30 volunteers (table 3).

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) [n=30].

Treatment	**AUC_T** ng/ml/h	**$C_{max,\ ss}$** ng/ml	$C_{min,ss}$ (ng/ml)	**t_{max}** h		$C_{average}$ (ng/ml)
Test	204.8 ± 71.1	15.6 ± 5.3	3.94 ± 1.70	6.5 ± 2.1 (3.0-11)		8.53 ± 2.96
Reference	202.0 ± 84.1	14.4 ± 6.5	4.10 ± 2.66	6.1 ± 2.9 (2.0-14)		8.42 ± 3.50
***Ratio (90% CI)**	1.03 (0.96-1.10)	1.11 (0.69-1.21)	1.05 (0.89-1.25)			
CV (%)	16.2 %	20.2 %	40.8 %			

AUC_T	area under the plasma concentration-time curve over the dosing interval
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{min,\ ss}$	minimum plasma concentration at steady state
t_{max}	time for average plasma concentration at steady state
$t_{1/2}$	half-life

**ln-transformed values*

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.

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 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 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.

PSUR cyclus and renewal date

The PSUR submission cycle is 3 years 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 until November 2009.

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

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Alfuzosine HCl Ranbaxy 10 mg is a generic form of Xatral 10 mg XR prolonged release tablets. Xatral 10 mg XR prolonged release 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 SPC 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 SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The concerned member states, on the basis of the data submitted, considered that Ranbaxy Belgie N.V. (Belgium) has demonstrated bioequivalence for Alfuzosine HCl Ranbaxy 10 mg prolonged release tablets with the reference product and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between the concerned member states was reached during a written procedure.

The following post-approval commitments were made during the procedure:
As the production method is defined to be non-standard by the fact that the tablets are prolonged-release tablets and a critical dosage form, and not manufactured by the use of any specific type of equipment, etc. The MAH has committed to submit new validation studies if the commercial batch size is increased.

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
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 procedure	Approval/ non approval	Assessment report attached