CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Alfuzosine HCl CF 10 mg, prolonged-release tablets Centrafarm Services 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/0677/01/MR
Registration number in the Netherlands: RVG 31128

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Pharmacotherapeutic group:	Drugs used in benign prostatic hypertrophy, alpha-adrenoreceptor antagonists
ATC code:	G04CA01
Route of administration:	oral
Therapeutic indication:	treatment of moderate to severe functional symptoms of benign prostatic hyperplasia (BPH)
Prescription status:	prescription only
Date of authorisation in NL:	26 July 2004
Concerned Member States:	Mutual recognition procedure with DE. Alfuzosine HCl Stada 10 mg has been withdrawn in DE (31-8-2006).
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 CF 10 mg, prolonged-release tablets from Centrafarm Services B.V., the Netherlands. The date of authorisation was on 26 July 2004 in the Netherlands.

The product is indicated for the 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, which is a racemate, is an orally acting quinazoline derivative, which selectively blocks post-synaptic alpha-1 receptors. In vitro studies have confirmed the selectivity of the substance on alpha-1 receptors in the trigone of the urine bladder, the urethra and the prostate gland. The clinical symptoms in benign prostatic hyperplasia are not only related to the size of the prostate, but also to sympathomimetic nerve impulses, which by stimulating the post synaptic alpha receptors increase the tension of the smooth muscle of the lower urinary tract. Treatment with alfuzosin relaxes this smooth muscle, thus improving the urinary flow.

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). This product is registered in the Netherlands since 1999, and a line extension of the product Xatral 2.5 mg. Xatral 2.5 mg has been authorised for more than 10 years in the EEA. 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 applicant has submitted a single and multiple dose bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Xatral LP 10 mg, prolonged-release tablets by Sanofi-Synthelabo, registered in France. 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 their 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 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.*). It is a racemate and several polymorphic forms are known: the anhydrous, mono-, di-, tri- and tetrahydrate modifications.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Quality control of drug substance
The active substance specification is adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional specifications for microbiological purity and particle size. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data have been obtained during storage at 25ºC/60% RH (18 months) and 40ºC/75% RH (6 months). The drug substance was packed in 2 PE bags in a PE drum. Sufficient information on the primary packaging material (LD-PE, meeting with Dir 90/128/EEC) is present. Based on the data submitted, a retest can be granted of 18 months when stored in the proposed packaging, protected from light and humidity.

**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
Each prolonged-release tablet contains 10 mg alfuzosin hydrochloride. The tablets are round, white, flat, bevelled-edged, and uncoated.

The excipients are: lactose monohydrate, hypromellose (E464), povidone K25 and magnesium stearate (E470b). The excipients used are well-known and safe in the proposed concentrations. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs.

Pharmaceutical development
The product is an established pharmaceutical form and its development has been described extensively in accordance with the relevant European guidelines. The tablets are packed in PVC (250 µm)/PVdC (60 g/m^2) –alu (20 µm) white opaque blister packaging. The PVC/PVdC film meets the requirements of Dir 90/128/EEC, identification of the PVC carrier film by IR and identification of the PVdC coating by the same method.

The aim for the formulation development was to mimick the (prolonged release) pharmacokinetic profile of the originator product allowing single (10 mg) daily dosing instead of dosing 3 times a day with the 2.5 mg immediate release tablets.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches in accordance with the relevant European guidelines. The MAH committed to provide transport validation data post-approval.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for appearance, dimensions, hardness, average and uniformity of mass, identification, water by KF, dissolution in pH 2.0, related substances, assay and microbiological purity. Limits in the specifications 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 for 3 pilot-scale batches have been provided, demonstrating compliance with the specifications.

Stability tests on the finished product

The tablets have been stored at 25ºC/60% RH (18 months) and 40ºC/75% RH (18 months), and were packed in PVC/PVdC-alu blister packaging during the stability tests. The 18 months results meet the set shelf life specifications. At 40ºC/75% RH no significant changes have been found. Based on the data submitted, the claimed shelf life of 30 months without specific temperature conditions was granted. The labelled storage conditions are: *"No special storage temperature"* and *"Store in the original package"*. The MAH committed to investigate the microbiological quality of the tablets for a shelf life moisture content of 12% post-approval.
The shelf life has been changed after marketing authorization by a type II variation (NL/H/0677/001/II/003) to 5 years with the special storage condition "*Do not store above 30 ºC*". The labelled storage conditions are: *"Do not store above 30 ºC"*.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM 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

This product is a generic formulation of Xatral, 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 identical products on the market. The approval of this product will not result in an increase in the total quantity of alfuzosin hydrochloride 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 a single and multiple dose bioequivalence study in which the pharmacokinetic profile of the test product Alfuzosine HCl CF 10 mg, prolonged-release tablets is compared with the French reference product Xatral LP 10 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 formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

The bioequivalence study was performed under fed conditions. Since the posology section of the innovator Xatral XR 10 mg states that the tablet is to be taken after the evening meal, this is considered acceptable.

Bioequivalence study
A randomised, open-label, 2-period cross-over combined single and 5-day multiple dose bioequivalence study was carried out under fasted conditions in 52 healthy male volunteers, aged 20-35 years. A single dose was administered at day 1, and multiple doses were administered from day 3 through day 7. The washout period between the two periods was 7 days. The tablets were administered with 240 ml water after a high-fat breakfast. Blood samples were taken predose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 24, 36, and 48 hours after single dose administration, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, and 24 hours after the last of the multiple daily doses.

Results
There was one drop-out due to personal reasons. The first 48 volunteers were scheduled for statistical analysis by protocol.

Table 1. Pharmacokinetic parameters (geometric mean (%CV), t_{max} (median, range)) of alfuzosin after single-dose administration under fed conditions

Treatment N=48	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	104.1 (48.0)	126.9 (47.1)	7.72 (37.8)	7.0 (3.0-12.0)	8.6 (42.7)
Reference	116.4 (47.6)	141.2 (45.6)	7.93 (35.7)	7.0 (1.0–14.0)	8.2 (31.4)
***Ratio (90% CI)**	--	0.90 (0.82-0.99)	0.97 (0.91-1.04)	--	--
CV (%)	--	28.0	18.9	--	--

$AUC_{0-\infty}$	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

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of alfuzosin after multiple-dose administration under fed conditions

Treatment N=48	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**t_{max}** h
Test	144.9 (38.3)	10.63 (32.0)	3.24 (59.8)	6.0 (1.0-12.0)
Reference	151.8 (30.6)	10.70 (24.4)	3.35 (62.4)	7.0 (2.0-12.0)
***Ratio (90% CI)**	0.96 (0.89-1.02)	0.99 (0.94-1.05)	0.97 (0.84-1.11)	--
CV (%)	20.8	16.4	41.9	--

AUC_τ	area under the plasma concentration-time curve over the dosing interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
t_{max}	time for maximum concentration

The 90% confidence intervals calculated for $AUC_{0-\infty}$, AUC_τ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25, both following single and multiple dose administration. Additionally, the C_{min} following multiple dose administration is within the 0.80-1.25 acceptance range. Based on the pharmacokinetic parameters of alfuzosin under fed conditions, it can be concluded that test Alfuzosine HCl CF 10 mg and the French reference Xatral LP 10 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. In the SPC is mentioned that alfuzosin should be used after a meal.

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 hydrochloride was approved in 1990 in the Netherlands, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of alfuzosin hydrochloride 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 applicant 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 Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the Dutch reference product Xatral, except for the administrative information.

Readability test
Not performed pre-licensing. The MAH committed to carry out user testing of the PIL (within 9 months) post-approval. The readability user testing was submitted in the type II variation (NL/H/0677/001/II/003).

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Alfuzosine HCl CF 10 mg, prolonged-release tablets have a proven chemical-pharmaceutical quality and are a generic form of Xatral XR 10 mg. 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 content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the Dutch reference product Xatral.

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.

The Board discussed the application during a Board meeting and followed the advice of the assessors and therefore authorised Alfuzosine HCl CF 10 mg in the Netherlands on 26 July 2004.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 21 December 2005. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Alfuzosine HCl CF 10 mg with the reference product, and have therefore granted a marketing authorisation.

The first PSUR cycle will cover a 6 months period. If applicable, an amendment of PSUR-periodicity to cover up to 3 years depending on the harmonised birth date of the corresponding innovator product may be considered in the assessment of the PSUR.

The date for the first renewal will be 9 February 2009. This renewal was submitted 3 October 2008. See Annex II.

The following post-approval commitments were made during the procedure.

Quality – drug product

- The MAH committed to provide transport validation data.
- The MAH committed to investigate the microbiological quality of the tablets for a shelf life moisture content of 12%.

Product information – PIL

- The MAH committed to carry out user testing of the PIL (within 9 months). The readability user testing was submitted in a type II variation (NL/H/0677/001/II/004). Commitment fulfilled.

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
Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material. Other cases.	NL/H/0677 /001/IA/ 001	IA	27-4-2006	11-5-2006	Approval	N
Minor change in the manufacture of the finished product.	NL/H/0677 /001/IB/ 002	IB	27-4-2006	17-5-2006	Approval	N
Withdrawal of the marketing authorization in Germany.	NL/H/0677 /001/MR	Withdrawal	---	31-8-2006	---	N
Extension of shelf life to 5 years, changing of storage conditions and minor changes to two test procedures.	NL/H/0677 /001/II/003	II	29-5-2008	19-11-2008	Approval	N
Update SPC and PIL including user testing.	NL/H/0677 /001/II/004	II	29-5-2008	19-11-2008	Approval	Y, Annex I
Change to comply with an update of the relevant monograph of the Ph.Eur. or national pharmacopoeia of a member state. Excipient.	NL/H/0677 /001/IA/ 005	IA	20-8-2008	3-9-2008	Approval	N
Renewal of the marketing authorisation accompanied by a type II variation.	NL/H/0677 /001/R/ 001	Renewal	3-10-2008	29-10-2008	Approval	Y, Annex II

Annex I – Variation NL/H/0677/001/II/004, Update SPC and PIL including user testing

I Scope of the variation

I.1 Regarding the SPC and the leaflet

The MAH has harmonized the SPC and leaflet with with the recently approved Day 90 texts of MR procedure NL/H/1327/001/MR.

I.2 Regarding the labelling and mockups

The MAH is requested to submit amended labelling text as well as new mockups in the national phase.

I.3 Readability test

The MAH submitted a readability test (this was a post-approval commitment). The RMS has assessed the readability test as provided by the MAH.

Population
The test persons were selected from an already existing database in which persons are listed that are generally interested in participation in user tests. These persons have already signed a generally applicable form declaring their consent and assuring confidentiality. In order to avoid that these persons learn how to handle a package leaflet it is not allowed that one person attends more than one user test within six months. This condition was followed strictly when selecting the test persons for this user test apart from three respondents who had participated in another user test only four months ago.

Method
The face-to-face interviews were carried out as described in the "*Readability Guideline*" (in particular Annex 2) and aimed to assess each respondent's ability to find and understand the information asked for.

Two rounds of readability testing were conducted in. The interviews were held in a separate room at the company YES Pharmaceutical Development Services GmbH in order to constitute a pleasant and quiet atmosphere.

Results
In the first round about 20% of the respondents were not able to locate the answer to question number 2 of the questionnaire. The MAH should have tried either to reword the question or to amend the leaflet for this specific point.
In test round 2 it appeared that 30% of the people had difficulty finding the answer th question 6 of the questionnaire. In the leaflet provide by the current MAH this sentence was deleted, which is acceptable. This is consitent with the currently approved day 90 texts (July 7th 2008 voor NL/H/1327/001/MR).

Conclusions
There are no concerns, although the leaflet will differ a bit as a result of the harmonisation with the day 90 leaflet of NL/H/1327/001/MR, a retest is not required at this moment. The readability test has been sufficiently performed.

II Overall conclusion

The variations are acceptable.

Annex II – Renewal marketing authorization

I.1 Introduction

Alfuzosine hydrochloride is an alpha-adrenoreceptor antagonist and is indicated for the treatment of moderate to severe functional symptoms of benign prostatic hyperplasia (BPH). Alfuzosine hydrochloride relaxes the smooth muscle in the prostate and bladder neck and thereby improves the urinary flow.
The product has been licensed via a Mutual Recognition Procedure with the Netherlands acting as Reference Member State.

For this renewal of the marketing authorization, the MAH has submitted the following documentation:

- Summary bridging report (SBR) covering the period 09-02-2004 until 09-06-2008
- PSUR 1 covering the period 9 February 2004 until 9 February 2006
- PSUR 2 covering the period10 February 2006 until 9 February 2007
- PSUR 3 covering the period 10 February 2008 until 9 February 2008
- Addendum report covering the period 10 February 2008 until 9 June 2008
- Clinical expert statement

I.2 Data review

World wide marketing authorisation status
The product has been approved in 15 countries worldwide and is marketed in 10 countries. The product was first approved on 9 February 2004 in the Netherlands. The product is registered through the mutual recognition procedure with the Netherlands as reference member state.

Update of regulatory authority or MAH actions taken for safety reasons
The following action has been taken for safety during the period under review. Upon class review of alpha-1-adrenoreceptor inhibitors in the PhVWP of the CHMP in November 2006 and a formal hearing with the MAHs in Germany, the German authority initiated a (graduate) plan procedure to mandate the amendment of the SOCs of alpha-1-adrenoreceptor antagonists including alfuzosin regarding the risk of intra-operative floppy iris syndrome (IFIS) during cataract surgery. After amendment of the SPC this procedure was closed.
Another procedure, regarding potential interactions with phosphodiesterase-5-inhibitors leading to hypotension is still ongoing. Upon request of the German Health Authority, drug interaction effects between alpha-blockers and phospodiesterase 5 inhibitors (PDE-5-inhibitors) were evaluated. During this evaluation no indication of such a drug interaction was identified in the scientific literature and the MAH did not consider an amendment of the RSI or SPC to be necessary. PSUR 3 mentions potential interactions with phosphodiesterase-5 inhibitors causing hypotension were addressed in a second (graduated) plan procedure. This topic is currently under discussion in the PhVWP. In case the conclusion of this discussion involves amendment to the SPC a type II proposal should be submitted within three months after finalisation of this discussion.
During the period covered by this report, there has been no marketing authorization suspension, no failure to obtain a marketing authorization renewal, no restrictions on distributions and no clinical trial suspension. There have been no dosage modifications, formulation changes, changes in target population or changes in indications.

Changes to reference safety information
During the period under review the CCSI (used as RSI) was amended. The latest version of the CCSI is dated August 2007. The amendment involved section 4.4 “Special warnings and precautions for use”, text regarding the risk of developing intra-operative floppy iris syndrome (IFIS) during cataract surgery associated with alpha-1-inhibitors was included. The MAH states that the listedness of the reported ADRs is determined against the reference safety information valid at the time of case entering into the database.

Adverse events

During the period under review a total of 8 cases including 15 adverse events were received. One of these adverse events was assessed as serious unlisted: toxic epidermal necrolysis (TEN). This case was received from the literature and concerned an 80 year old male patient who developed TEN during treatment with alfuzosin and subsequently died. Symptoms did not improve after alfuzosin discontinuation and treatment with IV hydrocortisones and supportive care in the ICU. Instead the patient's epidermal necrolysis progressed and he developed complications of pseudomonas bacteraemia, septic shock and renal failure. The authors stated that the diagnosis of alfuzosin-induced TEN was made based on the absence of the use of other concurrent medications and a 4-week interval of therapy initiation to the onset of event.

The MAH comments TEN is not a known adverse reaction known to the class of drug. The causal relationship was assessed probably related due to the temporal association and the absence of an alternative explanation. The MAH concludes this single case does not elicit a safety concern.

During the time period covered by the Summary Bridging Report, there were 30 non-serious, unlisted ADRs with Climodien reported to the MAH.

Conclusion

The MAH committed to monitor toxic epidermal necrolysis and discuss this topic in the next PSUR. In addition, the MAH was asked to sort out a discrepancy between PSUR1 and the summary bridging report.

Fatal cases

One case reporting a fatal outcome was received during the period under review. This case reported the adverse event TEN (already discussed under section "adverse events").

Studies

Newly analysed company-sponsored studies

The MAH states they did not perform any clinical, non-clinical or epidemiological study during the period under review which contains important safety information.

Targeted new safety studies

The MAH states that during the period under review no new studies were specifically planned or conducted to examine an actual or hypothetical safety study.

Published studies

The MAH states that during the period under review no study report containing important safety findings was published in the scientific literature.

Lack of efficacy

The MAH states no cases concerning "lack of efficacy" have been reported during the period under review.

Drug interactions

During the period under review the MAH received one non-serious case report on a suspected interaction with citalopram.

Overdose

The MAH states no cases concerning "overdose" have been reported during the period under review.

Abuse or misuse

The MAH states no cases concerning "abuse/misuse" have been reported during the period under review.

Medication errors

The MAH states no cases concerning "medication errors" have been reported during the period under review.

Special patient groups

The MAH states one case concerning acute hepatitis in an elderly patient with chronic liver disease was published in the scientific literature during the period under review. This case concerned an 80 year old male patient who developed acute hepatitis while receiving alfuzosin for benign prostatic hyperplasia. Co-medication included digoxin and aspirin. Symptoms improved after alfuzosin was discontinued. However, 18 weeks after alfuzosin withdrawal the patient was diagnosed to have child-phugh grade a chronic liver disease.

Conclusion
No actions are considered required. The medical condition of chronic liver disease provides a possible explanation for the event.

Pregnancy and lactation
The MAH states no cases concerning “”pregnancy and lactation” have been reported during the period under review.
Effects of long-term treatment
The MAH states no special findings after long-term treatment with alfuzosin have emerged during the period under review.

Product information
Although the amended terminology in section 4.8 is not fully in line with the MedRA terminology, it was accepted for the following reason: since the reference text (SPC of other alfuzosine product in the MRP procedure) includes similar terminology and this terminology will not influence the clinical impact of the SPC. However, this issue should be solved during the establishment of the CSP in the PSUR harmonisation project for alfuzosine products in November 2009.

Readability test
The RMS has assessed the readability test as provided by the MAH. There are no concerns, although the leaflet will differ a bit as a result of the harmonisation with the day 90 leaflet of NL/H/1327/001/MR, a retest will not be required at this moment.

Overall conclusion
No significant new information has been received regarding drug interactions, overdose, drug abuse or misuse, experience in special patient groups, effects of long-term treatment or on increased frequency of side effects.

Alfuzosine products take part in the PSUR synchronization project of the Heads of Medicines Agencies. In view of the EU worksharing project, the MAH is recommended to follow the harmonised birth data and it’s data lock point. The allocated first data lock point for alfuzosin products is November 2009. The next PSUR should therefore have November 2009 as data lock point.

The topic additive hypotensive effect due to interaction with PDE5 inhibitors is currently under discussion in the PhVWP. The MAH committed to submit a type II proposal in case the conclusion of this discussion involves amendments to the SPC.

The Medicines Evaluation Board followed the advice of the assessors. Agreement between member states was reached during a written procedure. The renewal procedure was finished on 29 October 2008.

The member states, on the basis of the data submitted, considered that a favourable benefit/risk ratio has been confirmed and have therefore granted renewal of the marketing authorisation with renewal date 9 February 2009.

I.3 Abbreviations

CCSI Company Core Safety Information
CSP Core Safety Profile
RSI Reference Safety Information
IFIS Intra-operative Floppy Iris Syndrome
TEN Toxic Epidermal Necrolysis