LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Alfuzosin Orion

(alfuzosin hydrochloride)

SE/H/1572/01-02/DC

This module reflects the scientific discussion for the approval of Alfuzosin Orion. The procedure was finalised on 2016-05-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Alfuzosin Orion, 2,5 mg, film-coated tablets and 10 mg, prolonged-release tablets, are generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xatral, 2,5 mg, film-coated tablets, authorised in UK since 2001, with Sanofi-aventis, UK as marketing authorisation holder.
The reference product used in the bioequivalence study is Xatral, 2,5 mg, film-coated tablets and Xatral XL, 10 mg, prolonged-release tablets, from UK with Sanofi-aventis, UK as marketing authorisation holder.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support this application one bioequivalence study with the 2.5 mg film-coated tablet and three bioequivalence studies with the 10 mg prolonged release tablet were submitted.

2.5 mg film-coated tablet:
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Alfuzosin, 2.5 mg, film-coated tablet with Xatral, 2.5 mg, film-coated tablet under fasting conditions. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of alfuzosin were determined with an adequately validated achiral LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Based on the submitted bioequivalence study, Alfuzosin Orion, 2.5 mg, film-coated tablet is considered bioequivalent with Xatral, 2.5 mg, film-coated tablet.

10 mg prolonged release tablet:
Bioequivalence was evaluated in three studies with the 10 mg prolonged release tablet formulation, one single-dose study under fasting conditions (222/08), one single-dose study under fed conditions (082/08) and one steady-state study under fed conditions (270/08).

Study 222/08: Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Alfuzosin, 10 mg, prolonged-release tablet with Xatral XL, 10 mg, prolonged-release tablet under fasting conditions. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of alfuzosin were determined with an adequately validated achiral LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study 082/08: Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Alfuzosin, 10 mg, prolonged-release tablet with Xatral XL, 10 mg, prolonged-release tablet under fed conditions. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of alfuzosin were determined with an adequately validated achiral LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study 270/08: Bioequivalence was evaluated in one two-way crossover steady-state study conducted in 38 healthy volunteers, comparing Alfuzosin, 10 mg, prolonged-release tablet with Xatral XL, 10 mg, prolonged-release tablet under fed conditions. One tablet of 10 mg of either test or reference was administered once a day in the morning (at an interval of 24 hours)

from dose 1 to dose 7 in each period. Blood samples were collected pre-dose on day 1 to day 7 and up to 24 hours after administration of dose 7 in both periods. The study design is considered acceptable. Plasma concentrations of alfuzosin were determined with an adequately validated achiral LC-MS/MS method. For $AUC_{\tau\,(ss)}$, $C_{max(ss)}$ and $C_{min(ss)}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Based on the submitted bioequivalence studies, Alfuzosin Orion, 10 mg, prolonged release tablet is considered bioequivalent with Xatral XL, 10 mg, prolonged-release tablet.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

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

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypotension, including orthostatic hypotension and concomitant use with alpha-1-blockers or other blood pressure lowering medicines • Administration in patients with hepatic insufficiency
Important potential risks	• Cerebral and cardiovascular ischemic disorders • QT prolongation • Intraoperative Floppy Iris Syndrome • Administration in elderly patients
Missing information	• Administration in patients with renal impairment

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: • Hypotension, including orthostatic hypotension and concomitant use with alpha-1-blockers or other blood pressure lowering medicines	Information given in SmPC sections 4.3, 4.4, 4.5, 4.7, 4.8 and 4.9. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important identified risk: • Administration in patients with hepatic insufficiency	Information given in SmPC sections 4.3 and 5.2. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important potential risk: • Cerebral and cardiovascular ischemic disorders	Information given in SmPC sections 4.4 and 4.8. Other routine risk minimisation measures: • Prescription only medicine	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Close monitoring through routine pharmacovigilance	
Important potential risk: • QT prolongation	Information given in SmPC sections 4.4. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important potential risk: • Intraoperative Floppy Iris Syndrome	Information given in SmPC sections 4.4 and 4.8. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important potential risk: • Administration in elderly patients	Information given in SmPC sections 4.2, 4.4 and 5.2. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Missing information: • Administration in patients with severe renal impairment	Information given in SmPC sections 4.4. and 5.2. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.

Summary of the RMP

The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Alfuzosin HCl 10 mg prolonged release tablets, NL/H/3015/001/MR. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Alfuzosin Orion, 2,5 mg, film-coated tablets and 10 mg, prolonged-release tablets, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The Decentralised procedure for Alfuzosin Orion, 2,5 mg, film-coated tablets and 10 mg, prolonged-release tablets, was positively finalised on 20160520.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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