

Public Assessment Report

Scientific discussion

Alfuzosin Stada

Alfuzosin hydrochloride

SE/H/559/01-02

This module reflects the scientific discussion for the approval of Alfuzosin Stada 5 mg and 10 mg tablets. The procedures were finalised at 2005-12-22 (10 mg) and 2006-02-23 (5 mg). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This generic application for marketing authorisation concerns Alfuzosin Stada, prolonged release tablets in the strengths 5mg and 10mg. The tablets are claimed to be essentially similar to Xatral, 5 mg, prolonged-release tablets and Xatral OD, 10mg, prolonged-release tablets marketed in Sweden by Sanofi-Synthelabo. The product is indicated for the treatment of moderate to severe functional symptoms of benign prostatic hyperplasia (BPH).

The reference products used in the bio-equivalence studies are Uroxatral S, 5mg, prolonged release tablets marketed by Sanofi-Synthelabo in Germany and Xatral LP, 10mg prolonged release tablets marketed by Sanofi-Synthelabo in France.

During the procedure, a potential serious risk to public health concerns was raised by one CMS and a CMD referral was initiated. A list of questions was agreed upon regarding a deficiency in the study design to evaluate the food effect of the 5 mg Alfuzosin Stada formulation. It was considered that, although deficiencies in the study design meant that an assessment of food effect could not be fully made, there was unlikely to be a serious risk associated with this medicinal product. The CMD referral was ended positively and approval could be granted by all concerned member states.

II. QUALITY ASPECTS

II.1 Introduction

Alfuzosin Stada is presented in the form of prolonged release tablets containing 5mg and 10mg of alfuzosin hydrochloride.

The excipients are hypromellose, lactose monohydrate, magnesium stearate and povidone.

The tablets are packed in PVC/PVDC aluminium blisters.

II.2 Drug Substance

Alfuzosin hydrochloride has a monograph in the Ph.Eur. and the manufacturer holds a CoS of the monograph (Certificate No. R0-CEP 2003-098 Rev 00). Alfuzosin hydrochloride is a white, crystalline powder which is freely soluble in water.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Alfuzosin Stada, prolonged release tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented comprise 36 months at 25°C and 6 months at 40°C. The data support the shelf life claimed in the SPC, 3 years with no special storage precautions.

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 Introduction

Alfuzosin is a blocker of post-synaptic alpha-1-receptors, and is used in benign prostata hyperplasia.

IV.2 Pharmacokinetics

Alfuzosin shows linear pharmacokinetics in the therapeutic dosage range. The kinetic profile is characterised by large interindividual fluctuations in plasma concentrations.

The bioavailability is 64% (45-90%) after administration of immediate release formulations. Peak plasma concentration is reached on average within 1.5 hours (range 0.5-6 hours) of administration of the dose. The bioavailability of the prolonged release tablets is somewhat lower than for immediate release tablets of 2.5 mg. Peak plasma concentrations are reached approx. 5 hours after intake.

Mean plasma half-life of alfuzosin is approximately 5 hours. Alfuzosin is extensively metabolised in the liver (several routes), metabolites are eliminated via renal excretion and probably also via biliary excretion. Of an oral dose, 75-91% is excreted in the faeces; 35% as unchanged substance and the rest as metabolites, indicating some degree of biliary excretion.

About 10% of the dose is excreted in urine as unchanged substance. None of the metabolites has any pharmacological activity.

In support of this application, one study on each strength 5 and 10 mg was submitted. The number of patients in the 5 mg study was 24 and 52 in the 10 mg fed study, however one subject discontinued due to personal reasons. In the 5 mg study, each period consisted of three phases: single dose phase, multiple dose phase and food effect phase. In the 5 mg study on day 1, a single oral dose was given after overnight fasting, and 14 blood samples were collected up to 30 h after administration. From day 3 to 7, twice daily dosing was performed. From day 3 to 6, pre-dose blood sampling was performed (C_{min}) for compliance testing. On day 7 the pharmacokinetic profile was performed from 11 blood samples collected up to 12 h after dose. On day 8, the dose was given after a standardised high-fat breakfast, and blood sampling was performed as on day 7. In the 10 mg study on day 1, a single oral dose was given after a standardised high fat breakfast, and 16 blood samples were collected up to 48 h after administration. From day 3 to 6, single daily dosing was performed. From day 3 to 6, pre-dose blood sampling was performed (C_{min}) for compliance testing. On day 7, dosing was performed after the high fat breakfast, and pharmacokinetic sampling was performed for 24 h (14 samples).

The primary pharmacokinetic parameters were C_{max} , C_{min} and AUC in both studies. In the **10 mg study**, all drug administrations were performed in the fed state.

During the procedure, questions were raised regarding the absence of data from single dose data for the 10 mg strength in the fasting state. An additional two-way randomised cross-over, two-period study was performed before the procedure started and was submitted and evaluated during the procedure. 36 subjects were included in this study, however one subject discontinued due to a viral infection not related to the treatment. Bioequivalence was concluded in the fasting state.

Bioequivalence was concluded for both strengths with respect to all relevant pharmacokinetic parameters, see tables below.

Single dose 5 mg, fasted conditions:

The results are given in the following table as geometric mean (CV%).

Preparation	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-∞} (ng*h/ml)
Test	8.7 (34%)	5.5	94 (36)
Reference	7.8 (31%)	5.2	95 (33)
Ratio	1.11		0.99
90% CI	1.02-1.22		0.88-1.12

Multiple doses 5 mg, fasted and fed conditions:

	AUC _τ (ng/ml*h)		C _{max} (ng/ml)		C _{min} (ng/ml)	
	Test	Reference	Test	Reference	Test	Reference
Fasted (day 7)	149.6	140.5	17.03	17.21	7.90	7.52
Fed (day 8)	144.97	149.65	17.63	17.46	8.56	9.14
90 % CI and point estimate Fasted conditions test/reference	1.065 (0.964-1.176)		0.990 (0.906-1.081)		1.05 (0.932-1.183)	
90 % CI and point estimate Fed conditions Test/reference	0.969 (0.897-1.047)		1.010 (0.909-1.122)			

Single dose 10 mg, fasted conditions:

The results are given in the following table as geometric mean (CV%). (n=35)

Preparation	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-t} (ng*h/ml)	AUC _{0-∞} (ng*h/ml)
Test	7.22 (51.6)	3.67 (1-8)	99.22 (50.1)	113.57 (50.3)
Reference	7.78 (55.4)	4.45 (2-10)	108.66 (46.9)	122.67 (44.0)
Ratio	0.93	-	0.91	0.93
90% CI	0.81-1.07*		0.80-1.05*	0.81-1.06*

*Parametric confidence intervals.

Single dose 10 mg, fed conditions:

The results are given in the following table as geometric mean (CV%).

Preparation	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-∞} (ng*h/ml)
Test	7.7 (38%)	6.7	104.1 (48%)
Reference	7.9 (36%)	7.4	116.4 (48%)
Ratio	0.98		0.90
90% CI	0.92-1.04		0.82-0.98

Multiple dose 10 mg, fed conditions:

The results are given in the following table as geometric mean (CV%).

Preparation	C _{max} (ng/ml)	C _{min} (ng/ml)	t _{max} (h)	AUC _τ (ng*h/ml)
Test	10.6 (32%)	3.2 (60%)	5.9	144.9 (38%)
Reference	10.7 (24%)	3.3 (62%)	6.7	151.8
Ratio	0.99	0.96		0.95
90% CI	0.94-1.05	0.84-1.10		0.89-1.02

However, a CMD referral followed the mutual recognition procedure due to deficiencies in the study design meant that an assessment of food effect could not be fully made of the 5 mg formulation. The food effect was not evaluated after a single dose, instead at steady state. The applicant modelled the possible underestimation of the food effect related to this formulation and found it to be around 8 % for the rate and extent of absorption. With the underestimation taken into account the rate and extent of absorption is within normal bioequivalence limits. It was concluded that, although there are deficiencies with the study design, the food effect is clinically irrelevant for Alfuzosin Stada 5 mg and the CMD referral was positively ended and approval could be granted for the lower strength as well.

IV.3 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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed. The applicant has made a commitment to perform user testing within 9 months after finalisation of the MR procedure.

The risk/benefit ratio is considered positive and Alfuzosin Stada, 5 mg and 10 mg, prolonged release tablets are recommended for approval.

Apart from the commitment made regarding the user testing of the package leaflet some commitments were made regarding the wording in the SPC section 4.2 and 4.4 and on the drug product. The applicant commits to further validate the shipment of the drug product from India to Europe. In case of increasing the drug product batches to the final specified batch size the applicant commits to further validate the manufacturing process of the drug product. Moreover, additional stability studies will be performed on bulk tablets if the holding time of the bulk tablets will increase four weeks above 30°C. Finally, the by the applicant, proposed new shelf life of 48 hours will be applied for in a variation procedure after approval.