Public Assessment Report

Scientific discussion

Alfuzosin "Merck NM"
Alfuzosin hydrochloride

DK/H/0899/001-002

This module reflects the scientific discussion for the approval of Alfuzosin "Merck NM". The procedure was finalised at 23 March 2006. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This generic application for marketing authorisation concerns Alfuzosin "Merck NM", prolonged release tablets in the strengths 5 mg and 10 mg. A national marketing authorisation in Denmark was granted on 5 September 2005. The tablets are claimed to be essentially similar to Xatral, 5 mg, prolonged-release tablets and Xatral Uno, 10 mg, prolonged-release tablets marketed in Denmark 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.

II. QUALITY ASPECTS

II.1 Introduction

Alfuzosin "Merck NM" is presented in the form of prolonged release tablets containing 5 mg and 10 mg of alfuzosin hydrochloride.
The excipients are lactose monohydrate, hypromellose, povidone and magnesium stearate.
The product is packed in PVC/PVDC/Aluminium blisters as primary packaging.

II.2 2.2 Drug Substance

Alfuzosin hydrochloride (INN, Ph. Eur.) is a white or almost white, crystalline powder which is freely soluble in water.
A CEP (Certificate No. R0-CEP 2003-098-Rev 00) has been issued for alfuzosin hydrochloride from the ASM. The CEP, incl. requirements for any other impurity and residual solvents, demonstrates the suitability of the Ph. Eur. monograph to control alfuzosin hydrochloride from the ASM.
The finished product manufacturer has established a specification for the active substance alfuzosin HCl. The specification requirements and analytical procedures incl. validation are in accordance with the CEP and Ph. Eur.
Satisfactory batch analyses results are included in the dossier.

II.3 Medicinal Product

The product is prolonged release tablets (the same as the Brand Leader) in 2 strengths: 5 mg and 10 mg alfuzosin hydrochloride per tablet, respectively. The formulation has been justified, and the function of the excipients, which all are of Ph. Eur. quality, has been explained. Appropriate BSE/TSE statements are included in the dossier and there is no BSE/TSE risk.
The manufacturing process has been sufficiently described and critical steps identified. The manufacture has been validated on 3 batches of both strengths. The results of the validation ensure that the manufacturing process consistently yields tablets of acceptable quality. All the results comply with the proposed specifications. The specifications are in accordance with Ph. Eur. and the relevant CHMP- and ICH-guidelines.
Stability studies under ICH conditions have been performed and the data presented support the shelf life claimed in the SPC, 30 months 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

IV.2.1 General description

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 approximately 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.

IV.2.2 Bioequivalence

In support of this application, one study on each strength 5 mg and 10 mg was submitted. 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.

Design 5 mg:
24 healthy adult male subjects participated in the study. All 24 subjects completed the study.
The study was a single centre, open label, balanced, randomised, 2 period, crossover combined single and multiple-dose study. The wash-out period was 7 days.

The study consisted of 3 phases:

- Single dose of 5 mg alfuzosin HCl (day 1) for assessing single dose pharmacokinetics.
- Five days of twice daily dosing (day 3 to 7) for assessing comparative bioavailability of the two formulations under steady-state conditions on day 7.
- Single dose (day 8) for assessment of effect of concomitant food intake on the pharmacokinetic profile of the formulations.

Phase I, single dose pharmacokinetics:
On day 1 a single dose was administered and subsequently a total of 14 blood samples were collected, a pre-dose sample as well as post dose samples at 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 15, 24 and 30 h post administration.
Phase II, multiple dose pharmacokinetics:
On day 2 no drug administration was performed. From day 3 to day 7 twice daily dosing was performed. From day 3 to day 6 pre-dose samples were collected (C_{min}). On day 7 11 samples were collected at administration (0 h) as well as 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 12 h post administration.
Phase III, food effect on multiple dose pharmacokinetics:
On day 8 a single dose was administered after a standardised high fat breakfast. 11 samples were collected at administration (0 h) as well as 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 12 h post administration.

Design 10 mg:
52 healthy adult male subjects participated in the study. One subject discontinued the study due to personal reasons.
The study was a single centre, open label, balanced, randomised, 2 period, crossover combined single and multiple-dose study. The wash-out period was 7 days.

The study consisted of 2 phases:

- Single dose of 10 mg alfuzosin HCl (day 1) for assessing single dose pharmacokinetics in the fed state.
- Five days of once daily dosing (day 3 to 7) for assessing comparative bioavailability of the two formulations under steady-state conditions in the fed state after administration on day 7.

Phase I, single dose pharmacokinetics:
On day 1 after a standardised high fat breakfast a single dose was administered and subsequently a total of 16 blood samples were collected, a pre-dose sample as well as post dose samples at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 18.0, 24.0, 36.0 and 48 h post administration.
Phase II, multiple dose pharmacokinetics:
On day 2 no drug administration was performed. From day 3 to day 6 single daily dosing was performed. From day 3 to day 6 pre-dose samples were collected (C_{min}). On day 7 a single dose was administered after a standardised high fat breakfast. 14 samples were collected at administration (0 h) as well as 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 18.0 and 24.0 h post administration.

Methods of analysis:
The plasma samples were analysed by a validated HPLC method with fluorescence detection for determination of alfuzosin concentrations.

Data analysis:
Parameters calculated:
Single dose, day 1: Primary parameters were C_{max}, AUC_t and AUC_{inf} (secondary: t_{max}, $t_{½}$, F_{rel}).
Steady state conditions: Day 3-6: C_{min}, day 7: C_{max}, C_{min} and AUC_τ (t_{max}, $t_{½}$).
Food effect, day 8 (only for **5 mg**): C_{max} and AUC_τ (t_{max}, $t_{½}$).

Statistical analysis:
ANOVA were performed on C_{max}, C_{min} and AUC_τ.
The secondary parameter t_{max} was not estimated due to practical considerations (a limited number of sampling points during the terminal phase due to the flat plasma concentration-time profile resulting from the extended release formulation).
Bioequivalence between test and reference formulation will be assumed if the 90% confidence interval for the ratio of geometric means for C_{max}, C_{min} and AUC_τ are within the acceptance range of 0.80-1.25 for AUC_τ and 0.75-1.34 for C_{max} and C_{min}.

Results/Discussion:
Single dose phase of the studies:
All primary parameters (C_{max}, AUC_t and AUC_{inf}) are comparable for the test and reference product, and the relative bioavailability F_{rel} indicates bioequivalence of the 2 formulations.
The extrapolated part of the AUC represents only 11% (5 mg) and 18% (10 mg) of the total AUC, indicating appropriate design of the studies.

Multiple dose phase of the studies:
The pharmacokinetic profiles are comparable for the test and reference product.
The CI's for the ratio of AUC_t, C_{max} and C_{min} are within acceptable range and stated by the study protocols (0.8-1.25 for AUC_t and 0.75-1.34 for C_{max} and C_{min}).
Concomitant food intake had no influence on the parameters C_{max} and AUC_τ comparing the test product in fed/fasted conditions, or comparing the test/reference product after food intake.
The AUC_τ indicates that total body clearance apparently decreases and/or bioavailability increases. However, as this effect is comparable for the test and reference product, the bioequivalence is not compromised by this fact.

For determination of bioequivalence only multiple dose data (fasting/fed) should be considered, since from a clinical point of view single dose data are of minor relevance for an active substance like alfuzosin, which is used in long-term therapy in a prolonged release drug product.

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.

Conclusion:
The test product, Alfuzosin prolonged release tablets 5 mg / 10 mg, can be considered bioequivalent to the reference product, brand Leader Xatral/Xatral Uno prolonged release tablets 5 mg / 10 mg.

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

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

The following commitments have been made by the applicant:

- The applicant enters into the commitment applying for provide results of user testing of the PIL by 6 months after day 90 of the procedure at the latest.
- The applicant enters into the commitment applying for a Type II variation within 60 days after day 90 to discuss the rewording of sections 2, 4.2 and 5.2 of the 5 mg and 10 mg SPC.
- The applicant enters into the commitment to submit the QP declarations (annex 6.22) from the batch release sites within 1 month.
- The applicant commits to place the first 3 production batches on long-term and accelerated stability studies.
- The applicant commits to perform a process validation study on the first 3 full-scale batches of Alfuzosin 10 mg and to submit the validation report as soon as available.
- The applicant commits to initiate additional stability data for bulk tablets if a holding time beyond 4 weeks at ambient temperatures, i.e. not more than 30°C, should be established.
- The applicant commits to re-evaluate the limits for related substances and water content, when stability data of Alfuzosin 10 mg full-scale batches will be available
- The applicant commits to submit the results of additional tests to clarify the discrepancy in mass balance during stability studies