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**Comparative randomized, single dose, two-way crossover open label study to determine the bioequivalence of two formulations of alfuzosin extended-release tablets**

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**Abstract**

**Objective**: Alfuzosin is a medication that is approved by the US FDA to treat benign prostatic hyperplasia (BPH) symptoms. The branded alfuzosin is expensive, hence, generic alfuzosin will provide better access to the medication, especially for non-insured patients with BPH. Bioequivalence studies are demanded by the regulatory authorities to allow the marketing of the new generics of alfuzosin. The aim of this report is to assess the bioavailability of the generic (test) and branded (reference) formulations of 10 mg alfuzosin extended-release (XR) tablets after oral administration to healthy adults under fed conditions. **Methods**: The current report methodology was based on a comparative randomized, single dose, two-way crossover open label study design. Thirty-three subjects were recruited and completed the clinical assessment. The pharmacokinetic parameters Crnax and AUC0→t, Kel, AUC0→∞, MRT, trnax,t1/2el were estimated to prove bioequivalence. **Results**: The confidence intervals for the log-transformed test/reference ratios for alfuzosin 110.65% (98.01-124.93) and 111.98% (101.87-123.10) for Cmax and AUC0→∞ respectively, which are within the allowed limits specified by the regulatory authorities (75-133% for Cmax and 80-125% for AUC0→∞). **Conclusions**: Clinically, the generic (test) formulation can be prescribed as an alternative to the reference for the indication of symptomatic treatment of BPH.

**Keywords**: Bioequivalence, alfuzosin, benign prostatic hyperplasia, BPH, pharmacokinetics

**Introduction**

Prostate enlargement or benign prostate hyperplasia (BPH) is a common problem in older men and associated with complications with lower urinary tract function such as frequent urination, incomplete emptying and nocturia. Therefore, quality of life is significantly impaired for millions of people worldwide suffering from this condition [1-2]. Benign enlargement of prostate tissue does not only cause physical obstruction of urethra, but also interferes with smooth muscle tone, which is controlled by the alpha 1-adrenergic receptors [3-4]. Therefore, alpha 1-blockers (AB), such as alfuzosin hydrochloride, represent the first line treatment for BPH to relive or reduce the symptoms rapidly through smooth muscle relaxation [5-6].

Alfuzosin hydrochloride or (RS)-N-[3-[(4-amino-6, 7- dimethoxy-2-quinozolinyl) methyl amino] propyl] tetrahydro-2-furanocarboxamide hydrochloride, is a highly selective AB that is absorbed efficiently after oral doses due to its high water solubility within the range of 10-20 ng/mL, as derived from its peak plasma concentration[7-10]. Alfuzosin is available as immediate and extended-release tablets. The latter has been presented to drive patient compliance within the elderly population, to aid their adherence to the treatment, and to manage the fluctuations of dosing of this short half-life drug of circa 3.8 hours [11]. Alfuzosin with an empirical formula of C19H27N5O4·HCL, is a white to off-white crystalline powder [12], that undergoes extensive first pass metabolism [13], and has a bioavailability of 60% with the controlled release dosage form of 10 mg per day dose [14-15]. The absolute bioavailability is affected largely by food. It has been reported to be around 49% under fed conditions, compared to 25% under fast conditions, presumably due to most of the absorption occurring at the duodenum-jejunum regions [16-17].

In this work, the bioequivalence between two formulations of the 10 mg extended-release tables of alfuzosin in healthy volunteers under fed conditions was conducted. The objective of this study was to investigate if the formulation developed at Tabuk Pharmaceuticals is equivalent to the currently marketed brand of Xatral® by Sanofi-Synthelabo to provide an alternative cost-effective dosage form.

**Method**

This study was designed as a single centre, open-label, randomized, single-dose study with two-way crossover design to compare the bioavailability of alfuzosin hydrochloride after administering a 10 mg XR tablet from two different manufactures. The originator Xatral by Sanofi-Synthelabo was designated the reference, and the XR tablet (alfuzosin), which is formulated by Tabuk Pharmaceuticals, was designated the test tablet. The clinical study was conducted on healthy adult subjects under fed conditions according to the International Conference of Harmonization (ICH) and Good Clinical Practice (GCP) guidelines[18]. The study was approved by the institutional review board of the International Pharmaceutical Research Centre (Amman, Jordan), where the study was conducted.

Healthy volunteers were approached to participate in this study. The participants had to meet the inclusion criteria illustrated in Table 1.

Table 1: Inclusion criteria to participate in the bioequivalence study.

In accordance with the ethical requirements, and to ensure the maximal safety margins of the participants, pregnant females and subjects with a history of the typical side effects of alfuzosin (asthma, peptic or gastric ulcer, sinusitis, pharyngitis, cardiovascular disorders, neurologic diseases and diabetes) were excluded from participating in thestudy.

All laboratory tests and data collection work was performed within 2 weeks prior to initiation of the clinical study. Laboratory tests included haematology, serology, biochemistry and urinalysis. The monitored vital signs included blood pressure, pulse, respiratory rate and body temperature. Subjects were informed about the aim of the study and potential risks associated with the study. Subjects agreed to and signed a written informed consent form before they were included in the study. The participants were free to withdraw at any time during the course of the study. All the included participants were instructed not to take any prescription or non-prescription medications 2 weeks prior to starting. Participants were instructed not to take any nutritional vitamins or consume large quantities of alcohol or beverages containing methyl-xanthine (eg coffee) 2 days prior to starting of the clinical study.

To control the feeding status of the participants, the composition, amount and timing of the meals were standardised for the participants. Subjects were administered a single dose of either the test or the reference product, as assigned by the randomization plan, with 240 mL of water, and instructed not to take water or fluids 1 hour before and after administration of the dose.

The participants were randomly divided into two groups, the reference group and the test group in the first phase of the trial, which was reversed after a 7-day washout period. In phase 1 of the study, the reference group received one 10 mg XR tablet of the reference alfuzosin, and the test group received a 10 mg XR test tablet. Blood samples (8mL) were collected at 0.00 (predose) and at 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 11.00, 12.00, 14.00, 16.00, 24.00, 36.00 and 48.00 hours post administration in lithium heparinized tubes, shaken gently and centrifuged at 3500 RPM for 10 minutes. After centrifugation, plasma samples were transferred into 5-mL plastic tubes and stored at -20°C until the time of analysis. A high-performance liquid chromatography-tandem mass spectrometry method (LC/MS/MS) was used to quantify alfuzosin in plasma samples. The bioanalytical method was adapted from another published work [19] and validated according to the ICH guidelines[20].

The pharmacokinetic parameters of alfuzosin were estimated using a standard non-compartmental model. The maximal plasma concentration (Crnax) and the time to peak plasma concentration (trnax) were estimated directly from the measured data. The area under the plasma concentration-time curve (AUC0→t) was calculated from measured data points of the concentration-time profile to the time of last quantifiable concentration (Clast) by the linear trapezoidal rule. The area under the plasma concentration-time curve extrapolated to infinity (AUC0→∞) was calculated according to the following formula:

AUC0→∞ = AUC0→t + Clast/[0.693/t1/2el ]

where Clast is the last quantifiable concentration. The elimination half-life (t1/2el) was calculated as:

t1/2el = 0.693/Kel

where Kel (the first-order elimination rate constant) was obtained as the slope of the linear regression of the Ln transformed plasma concentrations versus time in the terminal period of the plasma curve. The pharmacokinetic calculations were performed using the Kinetic 2000 computer program.

Finally, an analysis of variance (ANOVA) was applied to the results of AUC0→∞,AUC0→t,Crnax, trnax,t1/2el,Kel, LnCrnax and LnAUC0→t to test the effect of the period, subject (sequence) and treatment on the readings.

**Results**

Fifty-eight volunteers were screened, of whom 34 met the inclusion criteria. At a later stage, and before commencing the clinical study, one patient decided to withdraw from the trial. For pharmacokinetic evaluations, data from the 33 subjects who completed the crossover were included in the analysis. In this crossover study, all the participants were male, Caucasian and ranged in age from 19 to 42 years. Their body mass index (BMI) and body weight ranged from 19.1 to 29.6 Kg/m2 and 54 to 96 kg, respectively. Table 2 illustrates the demographic data for the participants.

Table 2: Demographic characteristics of the participants (median, upper and lower limit).

The mean plasma alfuzosin concertation-time profiles were similar for the 2 formulations of alfuzosin tablets. A slight increase in Cmax was noticed in the test product, however, this increase was statistically insignificant. The concentration-time profile of the two formulations of alfuzosin XR tablets is shown in Figure 1.

Figure 1: Concentration-time profile over 48 hours after administering 10 mg Alfuzosin XR reference (■) and test (▲) tablets. The insert shows the expanded 0-12 hr concentration time profile. (BLQ values at time 0 and 48 hr were set to zero).

Drug plasma levels were designated as surrogate parameters to indicate clinical activity. The pharmacokinetic parameters Crnax and AUC0→t were considered the primary indicators of bioequivalence, whereas Kel, AUC0→∞, tmax,t1/2el were considered secondary parameters to prove bioequivalence. The estimation of all the pharmacokinetic parameters was very close between the two formulations. Cmax and tmax were found to be 12.2 ng/mL, 7.0 hr, 13.4 ng/mL and 6.1 hr for the test and reference products, respectively.

The adjusted geometric mean ratios (test/ reference) of AUC0→t andCmaxfor the 2 alfuzosin XR formulations were within the allowed bioequivalence limit specified by the regulatory authorities (80-125% for AUC0→t and 75-133% for Cmax), as shown in Table 3.

Table 3: Bioequivalence confidence intervals of alfuzosin 10 mg tablet from the test versus the reference formulation.

The pharmacokinetic parameter estimates of alfuzosin10 mg XR reference and test tablets are shown in Table 4.

Table 4: Pharmacokinetics parameters of alfuzosin from 10 mg XR tablets (test

versus reference product).

ANOVA analysis of the log-transformed data and the untransformed pharmacokinetic parameters revealed no interference from the sequence effect, product or period effect on the pharmacokinetic parameters (see Table 5).

Table 5: P-values obtained from alfuzosin ANOVA results after an oral dose administration of one 10 mg tablet of test product and, alfuzosin reference product.

**Discussion**

This study was a single centre, open-label, randomized, single-dose study with two-way crossover design to compare the bioavailability of alfuzosin between of two products in healthy adult subjects under fed conditions.

The results of this bioequivalence study showed that the two studied products, the test and the reference 10 mg alfuzosin XR tablets, were bioequivalent under fed conditions. Furthermore, the two formulations can safely be used interchangeably by patients. The Reference Products were within the boundaries specified by the health regulatory authorities of 80-125% for AUC0→t and 75-133% forCmax because the parametric 90% confidence intervals of the mean values for the test/reference ratio were inside the bioequivalence acceptable boundaries for the two formulations of alfuzosin.

ANOV A analysis on the log-transformed data, Cmax and AUC0→t and untransformed data for Cmax, AUC0→t, AUC0→∞, Kel, t1l2eI and tmax showed that sequence effects and product or period effects for all these parameters did not significantly influence the outcome of the study. The mean plasma curves of both products were almost identical. However, the new alfuzosin formulation (test product) exhibited a minor increase in Cmax, which should not affect the efficacy or the safety of the new formulation.

As plasma levels are a meaningful surrogate for pharmacodynamic action and adverse events, this demonstrates that an equivalent therapeutic activity and tolerance are to be expected from *alfuzosin 10 mg* *XR tablets* and *Xatral 10 mg XR* tablets.

**Conclusion**

This clinical study clearly illustrates the bioequivalence of the two formulations of alfuzosin 10 mg XR tablets. All estimates of the tested pharmacokinetic parameters were almost identical between the two formulations of alfuzosin. The two formulations of alfuzosin tablets were well tolerated by all participants. There were no significant side effects or allergic reactions reported for any participant. The presence of a bioequivalent form of 10 mg alfuzosin tablets provides an affordable option, and increased access to the medication in patients with BPH.

**Declaration of Conflicting Interests**

The authors declare that they have no competing interests in this work.

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