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## Comparison of fixed dose combination of Alfuzosin and Solifenacin with individual marketed products

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**Background:** Benign prostatic hyperplasia (BPH) is a disorder that is manifested as a non-malignant enlargement of the prostate gland and caused by the progressive hyperplasia of prostatic cells. It leads to constriction of the urethral opening, and therefore, is often associated with lower urinary tract symptoms (LUTS). The medical therapies for treatment of BPH target to diminish bladder outlet obstruction. Alpha-adrenergic antagonists (alpha-blockers) and 5-alpha-reductase Inhibitors (5-ARIs) are the mainstay of pharmacotherapy of LUTS/BPH.

Overactive bladder (OAB) is a symptom complex manifested as urinary urgency, leading to increased urinary frequency and nocturia, often with urgency incontinence. Similar symptoms, such as bladder outlet obstruction (BOO) and detrussor overactivity (DO), are also seen in prostatic hyperactivity. Thus, both OAB and BPH may present as LUTS.

Since bladder contractions are mediated by acetylcholine, anticholinergic agents like solifenacin and tolterodine are used to reduce bladder smooth muscle contractility.

Combination therapy has been proven to relieve symptoms and delay progression of BPH and also when symptoms of OAB and LUTS/BPH are present. Hence, fixed dose combination (FDC) of alpha-adrenergic and anticholinergic agent (given once daily) is an attractive option for patients of BPH/LUTS with OAB. A fixed dose combination of Alfuzosin and Solifenacin has been developed for patients with LUTS/BPH alongside OAB. The pharmacokinetic parameters of Alfuzosin and Solifenacin were compared to establish bioequivalence between the fixed dose combination tablet of Alfuzosin Hydrochloride 10 mg Extended Release and Solifenacin Succinate 5 mg, against Xatral XL 10 mg tablets (containing alfuzosin hydrochloride prolonged release 10 mg) of Sanofi-Synthelabo Limited, United Kingdom (UK) and Vesicare 5 mg tablets (containing solifenacin succinate 5 mg) of Astellas Pharma Limited, UK administered concurrently. The study was conducted in healthy adult human subjects under fed conditions.

**Objective:** To assess the bioequivalence of fixed dose combination capsule of Alfuzosin hydrochloride 10 mg extended release and Solifenacin succinate 5mg of Ranbaxy Laboratories Limited, India and Xatral XL 10 mg tablets (Containing Alfuzosin hydrochloride prolonged release 10 mg) of Sanofi Synthelabo Limited, United Kingdom and Vesicare<sup>30</sup> 5 mg tablets (Containing solifenacin succinate 5 mg) of Astellas Pharma Limited, UK, in healthy, adult, male, human subjects, under fed condition.

**Methods:** The study was conducted as an open label, balanced, randomized, two-treatment, two-sequence, two-period, singledose, cross-over, bioequivalence study in forty-two (42) male subjects of Asian origin, who had given signed informed consent prior to enrolment into the study. A single oral dose of Reference products (Xatral XL 10 mg tablets and Vesicare 5 mg tablets) or Test formulation (a single oral dose of fixed dose combination capsule of Alfuzosin hydrochloride 10 mg extended release and Solifenacin succinate 5 mg) was administered to the subjects. The products were administered to the subjects under lowlight conditions, with 240 ml of drinking water. Both treatments were administered after consumption of a high-fat high-calorie breakfast.

The two treatments were separated by a washout period of 37 days.

Blood samples were collected pre-dose and up to 72 hours post dose in each period for determination of plasma alfuzosin and solifenacin concentrations and calculation of the pharmacokinetic parameters. ANOVA was performed on the log (natural)-transformed pharmacokinetic parameters. A 90% confidence interval for the ratios of the test and reference product averages (least square means) were calculated for alfuzosin and solifenacin to establish bioequivalence.

**Results:** The results of statistical analysis showed that 90% confidence intervals for both alfuzosin and solifenacin were within bioequivalence acceptance criteria of 80 to 125%. The 90% confidence intervals obtained for alfuzosin for  $C_{max}$ ,  $AU_{C0-1}$  and  $AU_{C0-1}$  were 102.74 – 122.75 %, 95.84 – 116.96 % and 95.82 – 116.76 %, respectively. The 90% confidence intervals obtained for solifenacin for  $C_{max}$ , and  $AUC_{0-72}$  were 89.55 – 97.91 % and 90.47 – 99.38 %, respectively. The two treatments were well-tolerated by the study subjects.

**Conclusion:** Based on these results, fixed dose combination tablet of Alfuzosin Hydrochloride 10 mg Extended Release and Solifenacin Succinate 5 mg, of Ranbaxy Laboratories Limited, India, and Xatral XL 10 mg tablets (containing alfuzosin hydrochloride prolonged release 10 mg) of Sanofi-Synthelabo Limited, UK and Vesicare 5 mg tablets (containing solifenacin succinate 5 mg) of Astellas Pharma Limited, UK administered concurrently are bioequivalent in healthy, adult, human male subjects under fed conditions.