

## **A COMPARISON OF THE PHARMACOKINETICS OF TROSPIUM CHLORIDE 60 MG EXTENDED RELEASE GIVEN UNDER A FASTED CONDITION TO THE PHARMACOKINETICS WHEN GIVEN WITH CONCURRENT ANTACID AND WHEN GIVEN WITH A HIGH-FAT MEAL.**

### Hypothesis / aims of study

Trospium chloride is a quaternary amine antimuscarinic approved at a dose of 20 mg twice daily (BID) for the treatment of overactive bladder (OAB). A once-daily (QD) formulation – trospium chloride extended release (XR) – is currently in development, which, once approved, will provide a valuable addition to the current selection of OAB therapies. The aim of this study is to compare the pharmacokinetics (PK) of trospium chloride XR 60 mg QD treatment under each of three conditions: fasted state, fasted state in conjunction with an antacid and fed condition (with a high fat meal).

### Study design, materials and methods

This is a single-center, single-dose, open-label, randomized, 3-period, 3-arm cross-over, bioavailability study in healthy male and female subjects to assess the PK effect of a fasted state, of food, or co-administration of an antacid and trospium XR 60 mg capsules. A total of 12 subjects are enrolled in the study (9 females, 3 males). The study consists of a Screening Period, 3 in-clinic Treatment Periods of approximately two (2) days per period, followed by 2 out-patient study visit days, and two 1-week Washout Periods.

Each subject is administered a single oral dose of trospium XR 60 mg under each of 3 conditions with 240 mL of water:

1. Treatment A: Under a fasted condition (control arm)
2. Treatment B: Under a fed (50% fat meal content) condition
3. Treatment C: Under a fasted condition co-administered with 20 mL Gaviscon Extra Strength Liquid

Trospium XR 60 mg is dosed 30 minutes following the start of the morning meal for the fed arm (Treatment B). Trospium XR 60 mg was to be dosed 30 minutes following the administration of 20 mL Gaviscon Extra Strength Liquid in the morning under fasted conditions (Treatment C). The assays of trospium in plasma will be performed under the responsibility of Prevalere Life Sciences.

Statistical methods included the calculation of arithmetic means, standard deviations, coefficients of variation, median, minimum, maximum and geometric means for the pharmacokinetic parameters. General methods of statistical bioequivalence were utilized to allow for descriptive comparison of the rate and extent of absorption of trospium using pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$ .  $T_{max}$  was also assessed. The Treatments were to be declared to have similar rates and extents of absorption if the point estimates for  $C_{max}$  and  $AUC_{0-\infty}$  were similar per bioequivalence methods (i.e., by a comparison of the ratio of means to a predefined confidence interval [80%, 125%]). Due to the limited sample size (N=12 subjects), the protocol stated that formal bioequivalence would, however, be assumed if the point estimates of the ratios fell within these bounds. It was not expected, due to the relative high variability of trospium concentrations within subjects and the limited sample size, that formal bioequivalence could be concluded from this study.

### Results

Eleven of the 12 patients had complete data available for analysis. The average concentration-time curve for the 3 dosing arms is provided below, along with a table of the ratios of the geometric mean pharmacokinetic parameters for the antacid and fed arms as compared to the fasted arm. A ratio near 100 indicates a similar parameter, while ratios further from 100 indicate differing parameters.

Figure 1: Mean Trospium Concentration (pg/mL) Over Time (N=11 Subjects)

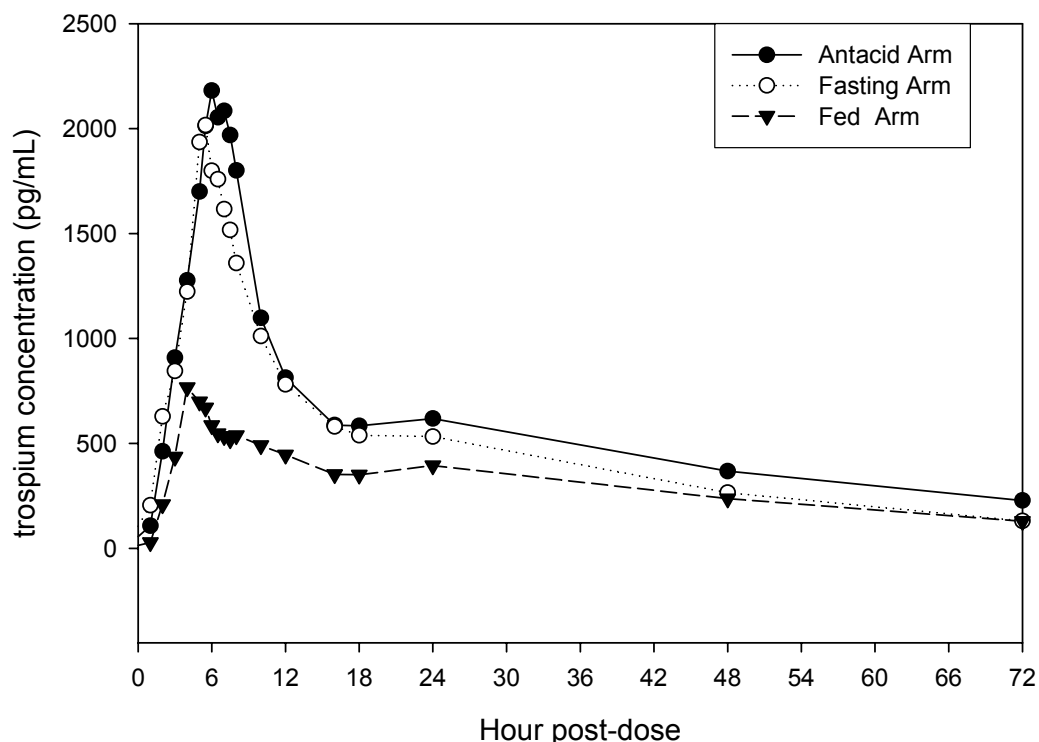


Table 1: Geometric Mean (Natural-Log Transformed) Pharmacokinetic Parameters of Antacid Condition and Fed Condition When Compared to Fasting Condition (Ratios of Geometric Means)

Dependent	Test	Ratio[%Ref]	Lower Bound of 90% CI	Upper Bound of 90% CI
Ln(AUC <sub>0-24</sub> )	antacid	107.48	73.68	156.80
	fed	56.18	38.51	81.96
Ln(AUC <sub>last</sub> )	antacid	111.36	82.62	150.10
	fed	67.62	50.17	91.14
Ln(C <sub>max</sub> )	antacid	102.51	65.09	161.46
	fed	42.99	27.29	67.70
Ln(T <sub>max</sub> )	antacid	124.53	93.07	166.61
	fed	153.57	114.78	205.47

**Interpretation of results**

The concentration-time curve revealed similar concentration profiles between the fasted arm (the control arm) and the antacid arm. The antacid arm demonstrated a slight higher C<sub>max</sub> (approximately 3-6% higher), and a slightly higher AUC (approximately 8-10% higher), and a slightly longer half-life than the fasted arm. However, given the limited sample size of 11 subjects, these differences were not statistically meaningful, and were further judged not to be clinically meaningful.

The fed arm demonstrated significantly lower C<sub>max</sub> and AUC than that for the fasted arm.

**Concluding message**

Trospium XR 60 mg given with antacid provided a similar concentration-time PK profile as that when trospium chloride was given under a fasted condition. Thus, trospium XR 60 mg can be given with no regard to antacid consumption. However, due to the limited sample size and high variability of the concentration data, formal bioequivalence could not be concluded.

Trospium XR 60 mg given with a high-fat meal provided a lower concentration-time PK profile as that when trospium was given under a fasted condition. Thus, trospium XR 60 mg should be given with regard to meals.

**FUNDING:** Indevus Pharmaceuticals

**DISCLOSURES:** Paid Employee

**CLINICAL TRIAL REGISTRATION:** This clinical trial has not yet been registered in a public clinical trials registry.

**HUMAN SUBJECTS:** This study was approved by the Arkansas Research Institutional Review Board Human Volunteers Research Committee and followed the Declaration of Helsinki Informed consent was obtained from the patients.