DARIFENACIN HAS NO CLINICALLY RELEVANT EFFECT ON WARFARIN OR DIGOXIN PHARMACODYNAMICS/ KINETICS IN HEALTHY MALES

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Darifenacin is a muscarinic M3 selective receptor antagonist developed for the treatment of overactive bladder (OAB). OAB is common in older patients, who may also receive warfarin or digoxin. As darifenacin is a substrate for cytochrome P450 (CYP) enzymes 2D6 and 3A4, and for the p-glycoprotein pump (p-gp) (Skerjanec et al., 2004), interactions with other substrates such as warfarin (CYP3A4) and digoxin (p-gp) are possible. Potential interactions have been investigated in two double-blind, placebo-controlled studies in healthy male subjects aged 18–45 years.

In a two-way crossover study, 14 subjects received darifenacin 30 mg once daily (od) or placebo for 11 days each, separated by a 7-day washout period. Warfarin was administered as a single 30 mg dose on Day 6 of each treatment period. Prothrombin time was measured at baseline, immediately prior to warfarin dosing, and at intervals up to 6 days after warfarin dosing. In a separate parallel group study (n=24), digoxin was administered for 17 days (0.25 mg od), with darifenacin 30 mg od or placebo on Days 8 to 17. Steady-state pharmacokinetics were assessed on Days 7 and 17.

Darifenacin did not significantly alter the area under the effect curve (AUEC) for warfarin (2,128 seconds x hours (sec.h), versus 2,111 sec.h with placebo; p=0.60) or maximum change from baseline in prothrombin time (9.0 and 9.6 seconds, respectively; p=0.08). The Day 7:17 ratios for digoxin exposure were 1.13 in the darifenacin-treated group and 0.98 with placebo, indicating a 15.6% increase (90% confidence interval [CI]: 8.3, 23.4) in digoxin exposure with darifenacin relative to placebo. The maximum plasma digoxin concentration was 19.6% higher (90% CI: 6.0, 35.0) on darifenacin than placebo, with Day 7:17 ratios of 1.06 and 0.89, respectively.

The most common treatment-related adverse events (AEs) in the warfarin study were dry mouth (11 darifenacin-treated subjects and 3 placebo recipients) and constipation (8 and 2 subjects, respectively). In the digoxin study, dry mouth was the most frequently reported AE (10 and 3 darifenacin- and placebo-treated subjects, respectively), followed by headache, which had a similar incidence in the two groups (6 and 5 subjects, respectively). The high incidence of dry mouth in darifenacin-treated groups may reflect the use of a high darifenacin dose (twice the maximum marketed dose). One darifenacin-treated subject withdrew from each study, due to a flu syndrome and vomiting/dyspepsia, both considered treatment related by investigators. There were no serious AEs.

Darifenacin, at twice the maximum marketed dose, had no statistically or clinically significant effect on warfarin pharmacodynamics. A slight increase in digoxin exposure was observed, but this does not preclude darifenacin use in patients taking digoxin. Digoxin levels should, however, be monitored when initiating, ending or changing the dose of darifenacin.