Effect of Rifampin on the Pharmacokinetics of Ertugliflozin in Healthy Subjects

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ABSTRACT

Purpose: Ertugliflozin is a selective sodium glucose cotransporter 2 inhibitor being developed for the treatment of type 2 diabetes mellitus. The primary enzyme involved in the metabolism of ertugliflozin is uridine diphosphate-glucuronosyltransferase (UGT) 1A9, with minor contributions from UGT2B7 and cytochrome P450 (CYP) isoenzymes 3A4, 3A5, and 2C8. Rifampin induces UGT1A9, UGT2B7, CYP3A4, and CYP3A5. Because concurrent induction of these enzymes could affect ertugliflozin exposure, this study assessed the effect of multiple doses of rifampin on the pharmacokinetic properties of single-dose ertugliflozin.

Methods: Twelve healthy adult subjects were enrolled in this open-label, 2-period, fixed-sequence study and received ertugliflozin 15 mg on day 1 of period 1, followed by rifampin 600 mg once daily on days 1 to 10 in period 2. On day 8 of period 2, ertugliflozin 15 mg was coadministered with rifampin 600 mg. Plasma samples for ertugliflozin pharmacokinetic analysis were collected during 72 hours after dosing on day 1 of period 1 and day 8 of period 2 and analyzed using a validated HPLC-MS/MS method. Pharmacokinetic parameters were calculated using noncompartmental analysis of concentration-time data. Natural log transformed $AUC_{0-\infty}$ and C_{max} of ertugliflozin were analyzed using a mixed-effects model with treatment as a fixed effect and subject as a random effect.

Findings: After administration of ertugliflozin 15 mg alone or with rifampin, the T_{max} was 1 hour. The mean $t_{1/2}$ was 12.3 hours for ertugliflozin alone and 9.2 hours with steady-state rifampin. Geometric mean ratios for $AUC_{0-\infty}$ and C_{max} were 61.2% (90% CI, 57.2%−65.4%) and 84.6% (90% CI, 74.2%−96.5%), respectively. Ertugliflozin was well tolerated when administered alone or with rifampin.

Implications: Coadministration of ertugliflozin with rifampin decreased ertugliflozin $AUC_{0-\infty}$ and C_{max} by 39% and 15%, respectively. The effect of the reduced exposure was evaluated using the ertugliflozin dose-response model. The model predicted that a 5-mg ertugliflozin dose after coadministration with rifampin is expected to maintain clinically meaningful glycemic efficacy. Therefore, no dose adjustment of ertugliflozin is recommended when ertugliflozin is coadministered with a UGT and CYP inducer, such as rifampin. (*Clin Ther*. 2018;XX:XXX−XXX) © 2018 Elsevier HS Journals, Inc. (*Clin Ther*. 2018;■:1−10) © 2018 Elsevier Inc. All rights reserved.

Key words: coadministration, ertugliflozin, pharmacokinetics, rifampin.

INTRODUCTION

The sodium glucose cotransporter2 (SGLT2) is a low-affinity, high-capacity, sodium-dependent glucose cotransporter that is expressed mainly in the proximal tubule of the nephron and is responsible for approximately 90% of renal glucose reabsorption.[1] SGLT2 inhibitors reduce renal glucose reabsorption, thereby increasing urinary glucose excretion and reducing plasma glucose and glycated hemoglobin (HbA_{1c}) levels in patients with type 2 diabetes mellitus (T2DM).

Ertugliflozin is a highly selective and potent SGLT2 inhibitor that is being developed for the treatment of adults with T2DM.[2,3] Phase III studies in patients with

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T2DM have found that once-daily ertugliflozin doses of 5 and 15 mg significantly reduced HbA_{1c}, decreased weight and blood pressure, and were well tolerated.[4–6]

The pharmacokinetic properties of ertugliflozin are similar in healthy subjects and in patients with T2DM. The oral absorption of ertugliflozin is rapid, with a median T_{max} occurring approximately 1 hour after dosing in the fasted state and approximately 2 hours after dosing in the fed state. The absolute bioavailability of ertugliflozin is approximately 100%, and its exposure increases in a dose-proportional manner over a dose range of 0.5 to 300 mg (data on file). In healthy volunteers, the $t_{1/2}$ of ertugliflozin ranges from 11 to 17 hours.[2] The mean $t_{1/2}$ of ertugliflozin is 14.6 hours in patients with T2DM and normal renal function.[7]

Overall, ertugliflozin exposure has low intersubject (%CV <22%) and intrasubject (%CV <10%) variability. On the basis of the population pharmacokinetic analysis of ertugliflozin, intrinsic factors, such as sex, race, age, weight, and patient status, do not have a clinically meaningful effect on the pharmacokinetic properties of ertugliflozin.[8] Therefore, no dosage adjustments are recommended based on sex, race, age, weight, or patient status.

Ertugliflozin is metabolized primarily by uridine diphosphate-glucuronosyltransferase (UGT) 1A9 with minor contributions from UGT2B7 and cytochrome P450 (CYP) isoenzymes 3A4, 3A5, and 2C8.[3] Inhibitors or inducers of individual UGT and CYP isozymes are not expected to have a significant effect on the exposure of ertugliflozin, and the results of in vitro studies suggest that clinical drug-drug interactions (DDIs) via ertugliflozin-mediated inhibition or induction of CYP isozymes or transporters are not anticipated.[2] However, it is possible that concurrent induction of multiple enzymes (UGTs and CYPs) could alter ertugliflozin exposure. Therefore, a DDI study evaluating the effect of a nonselective enzyme inducer on the clinical pharmacokinetic properties of ertugliflozin was conducted. Rifampin (rifampicin), a prototypical enzyme inducer, was selected for use in this study because it clinically induces UGT1A9, UGT2B7, CYP3A4, and CYP3A5,[9] with near-maximal effects anticipated after continuous dosing for 7 days.

In vitro studies using Madin-Darby canine kidney cells transfected with multidrug resistance 1 (also known as P-glycoprotein [P-gp]) or *BCRP* gene indicated that ertugliflozin is a substrate for P-gp and *BCRP*-mediated efflux. However, the oral bioavailability of ertugliflozin is approximately 100%, and dose-proportional increases in exposure over the dose range of 0.5 to 300 mg are observed. Therefore, neither P-gp nor *BCRP* is likely to be a limiting factor for oral absorption of ertugliflozin, and inhibition of these transporters is unlikely to meaningfully increase ertugliflozin exposures at therapeutic doses. Ertugliflozin has also been extensively evaluated in organic anion-transporting polypeptide (OATP)-transfected human kidney embryo 293 cells and is not considered a substrate of hepatic OATP1B1, OATP1B3, and OATP2B1 uptake transporters; therefore, a clinically relevant DDI of ertugliflozin with OATP inhibitors is not expected.

This DDI study evaluated the effect of enzyme induction on ertugliflozin exposure with no contribution from OATP inhibition by rifampin. It was conducted to assess the effect of multiple doses of rifampin on the plasma pharmacokinetic properties of ertugliflozin by comparing the exposure of a single 15-mg dose of ertugliflozin administered under fasted conditions to healthy volunteers in the presence and absence of steady-state enzyme induction by rifampin.

PATIENTS AND METHODS

Study Objectives

The primary objective of the study was to estimate the effect of multiple doses of orally administered rifampin on the pharmacokinetic properties of single-dose (15 mg) ertugliflozin. The secondary objective was to determine the tolerability of ertugliflozin 15 mg when administered alone or in combination with rifampin 600 mg once daily for 10 days. A total dosing duration of 10 days for rifampin was used to ensure that enzyme induction attributable to rifampin could be maintained and evaluated during the entire pharmacokinetic sampling interval after concomitant administration of ertugliflozin.

Participants

Healthy male and/or female subjects of nonchildbearing potential aged 18 to 55 years, with a body mass index of 17.5 to 30.5 kg/m^2 and a total weight >50 kg (110 lb), who had provided a signed, dated informed consent form and were willing and able to comply with the study plan were enrolled into the study. Subjects with the following were not eligible to participate in the study: positive urine screen result for