# Investigation of Potential Pharmacokinetic Interactions Between Teneligliptin and Metformin in Steady-State Conditions in Healthy Adults

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## ABSTRACT

**Purpose:** We assessed the effects of coadministration of metformin and teneligliptin on their pharmacokinetics in steady-state conditions relative to the administration of either drug alone.

**Methods:** This was a Phase I, single-center, open-label, 2-way parallel-group study in healthy male and female subjects. Subjects in group 1 (n = 20) were administered 40 mg of teneligliptin once daily for 5 days, and 850 mg of metformin BID was added to ongoing teneligliptin for an additional 3 days. The subjects in group 2 (n = 20) were administered 850 mg of metformin BID for 3 days, and 40 mg of teneligliptin once daily was added to ongoing metformin for an additional 5 days. Pharmacokinetic outcomes were the $AUC_{0-\tau}$ and $C_{max}$ of metformin and teneligliptin when administered alone or in combination.

**Findings:** Ten male and 10 female subjects participated in each group (mean ± SD age 39.2 ± 11.6 years [range, 19–63 years] in group 1, 47.6 ± 11.9 years [27–64] in group 2; mean ± SD BMI 23.36 ± 2.45 in group 1, 24.56 ± 2.54 in group 2). One female subject in each group was withdrawn because of an adverse event (AE) (vomiting). All 20 subjects in each group were included in the safety analyses, and 19 subjects in each group were included in the pharmacokinetic analyses. The geometric least square means ratio (teneligliptin plus metformin/teneligliptin alone) for $C_{max}$ and the $AUC_{0-\tau}$ for teneligliptin were 0.907 (90% CI, 0.853–0.965) and 1.042 (90% CI, 0.997–1.089), respectively. The geometric least square means ratio (metformin plus teneligliptin/metformin alone) for the $C_{max}$ and $AUC_{0-\tau}$ for metformin were 1.057 (90% CI, 0.974–1.148) and 1.209 (90% CI, 1.143–1.278). The 90% CIs were within the prespecified threshold for equivalence (0.80–1.25), except for the $AUC_{0-\tau}$ for metformin, which was increased by teneligliptin by 20% relative to metformin alone. In group 1, nine subjects experienced 25 AEs during treatment with teneligliptin alone and 10 subjects experienced 15 AEs during treatment with teneligliptin plus metformin. In group 2, eight subjects experienced 11 AEs during treatment with metformin alone and 11 subjects experienced 18 AEs during treatment with metformin plus teneligliptin. Two AEs in each treatment group were rated as severe. Results of in vitro experiments suggest that teneligliptin-mediated inhibition of organic cation transporter-2 does not increase metformin exposure.

**Implications:** Coadministration of teneligliptin and metformin was well tolerated by these healthy subjects during the 8-day treatment period. Coadministration with metformin did not affect the pharmacokinetics of teneligliptin. Although coadministration with teneligliptin increased exposure to metformin, this change is unlikely to be clinically relevant. European Clinical Trials Database identifier: 2007-001511-29. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) 

**Key words:** dipeptidyl peptidase-4 inhibitor, drug–drug interactions, metformin, pharmacokinetics, teneligliptin.

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## INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the small intestine in response to meal ingestion.[1] GLP-1 is important in regulating postprandial blood glucose levels because it stimulates insulin secretion in a glucose-dependent manner and inhibits glucagon secretion.[2] Despite its unique nature and desirable effects, which include enhancing pancreatic β-cell mass, inhibiting gastric emptying, and reducing food intake,[3–6] the clinical use of GLP-1 is restricted because of its short half-life, caused by its rapid degradation by dipeptidyl peptidase-4 (DPP-4).[7,8] Therefore, DPP-4 inhibition has been accepted as a reasonable target for enhancing GLP-1 action and lowering blood glucose in a glucose-dependent manner.

Teneligliptin, a DPP-4 inhibitor, is rapidly absorbed in humans, and its plasma concentration profile exhibits biphasic elimination. It reaches steady state within ~5 days after starting administration at a dose of 40 mg once daily (data on file). Approximately 66% of teneligliptin is eliminated by hepatic metabolism, and the remainder is excreted in urine. The major enzymes involved in the metabolism of teneligliptin are cytochrome P450 (CYP) 3A4 and flavin-containing monooxygenase 3 (FMO3). The metabolites produced by CYP3A4 and FMO3 are related to thiazolidine-1-oxide derivatives.[9] An in vitro study using human P-glycoprotein (P-gp)-expressing cells also showed that teneligliptin is a substrate of P-gp.[10] Coadministration of teneligliptin with ketoconazole (a strong inhibitor of CYP3A4 and P-gp) to healthy subjects and to patients with renal impairment increased teneligliptin exposure by 1.5 and 1.7 times, respectively, compared with teneligliptin alone in healthy subjects.[10,11] Renal excretion and hepatic metabolism of teneligliptin mediated by CYP3A4 and FMO3 are important determinants of the plasma concentrations of teneligliptin. We predicted that each of these 3 pathways for teneligliptin elimination (renal excretion, hepatic metabolism by CYP3A4, and hepatic metabolism by FMO3) contributes to ~30% of the systemic clearance.[12] Therefore, we believe that exposure is not markedly increased in patients with strong CYP3A4 activity, P-gp inhibition, or renal disorders.

Metformin, an oral antidiabetic agent belonging to the biguanide group, has been used for the treatment of type 2 diabetes for >40 years. It improves glucose tolerance in patients with type 2 diabetes by lowering basal and postprandial plasma glucose concentrations. Metformin's pharmacologic mechanisms of action differ from those of other classes of oral antidiabetic agents. It decreases intestinal absorption of glucose and hepatic glucose synthesis and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. When used alone, metformin does not cause hypoglycemia in patients with type 2 diabetes or in healthy subjects. According to the approved label for metformin hydrochloride,* the recommended dosage of metformin is 500 mg or 850 mg BID or TID.[13] $C_{max}$ of metformin is reached ~2 to 3 hours after oral administration. The absolute bioavailability of metformin when administered as a 500-mg tablet is reportedly between 50% and 60%. Approximately 20% to 30% of the administered dose is not absorbed and is excreted in feces.[14] Metformin reaches steady-state conditions within 24 to 48 hours after starting administration at clinically approved doses.[13] The absorption of metformin after an oral dose is incomplete and exhibits saturation characteristics.

It is believed that the absorption of metformin displays nonlinear pharmacokinetics. Although the absorption of metformin is reduced and slightly delayed by food intake, metformin should be taken together with or after a meal to improve its gastrointestinal tolerability. Metformin shows negligible binding to plasma proteins. No metabolites of metformin have been identified in humans. Metformin is excreted unchanged in urine, and its renal clearance is >400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. The renal excretion of metformin involves organic cation transporter-2 (OCT2), multidrug and toxin extrusion (MATE) 1 and MATE2-K.[15–17] In patients with impaired renal function, the renal clearance of metformin is decreased in proportion to that of creatinine, prolonging the $t_{1/2}$ and increasing the plasma metformin concentration.

Teneligliptin is prescribed either as monotherapy or in combination with other oral antidiabetic drugs for the treatment of type 2 diabetes. In many countries, metformin is the most commonly prescribed oral antidiabetic drug,[18] and it is likely to be coadministered with teneligliptin. For this reason, it is important to ensure that there are no interactions

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