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# Drug interactions of dipeptidyl peptidase 4 inhibitors involving CYP enzymes and P-gp efflux pump

# Maideen NMP. Drug interactions of DPP4 inhibitors

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**Abstract**

Dipeptidyl peptidase 4 (DPP4) inhibitors are oral antidiabetic drugs approved to manage type 2 diabetes mellitus. Saxagliptin is a substrate of CYP3A4/5 enzymes while other DPP4 inhibitors such as sitagliptin, linagliptin, gemigliptin and teneligliptin are weak substrates of CYP3A4. DPP4 inhibitors have also been identified as substrates of P-gp. Hence, the drugs inhibiting or inducing CYP3A4/5 enzymes and/or P-gp can alter the pharmacokinetics of DPP4 inhibitors. This review is aimed to identify the drugs interacting with DPP4 inhibitors. The plasma concentrations of saxagliptin have been reported to be increased significantly by the concomitant administration of ketoconazole or diltiazem while no significant interactions between various DPP4 inhibitors and drugs like warfarin, digoxin or cyclosporine have been identified.

**Key words:** Drug interactions; Sitagliptin; Saxagliptin; Linagliptin; Gemigliptin; Teneligliptin; Vildagliptin; Anagliptin; CYP3A4; P-gp efflux pump

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**Core tip:** The probability of adverse drug interactions is higher among diabetic patients due to the concomitant administration of antidiabetic drugs with multiple medications to treat comorbidities such as hypertension, dyslipidemia, other cardiovascular problems, infections, depression, and others. Dipeptidyl peptidase 4 (DPP4) inhibitors are oral antidiabetic drugs approved to manage type 2 diabetes mellitus. Some of the DPP4 inhibitors have been identified as substrates of CYP3A4/5 enzymes and P-gp efflux pump. The drugs inhibiting or inducing CYP3A4/5 enzymes and/or P-gp can alter the pharmacokinetics of DPP4 inhibitors. The prescribers and the pharmacists are required to be aware of the drugs altering the pharmacokinetics of DPP4 inhibitors significantly to prevent adverse drug interactions.

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**INTRODUCTION**

Dipeptidyl peptidase 4 (DPP4) inhibitors are oral antidiabetic drugs approved to manage type 2 diabetes mellitus. The members of this class include sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin and alogliptin. DPP4 enzyme is involved in the biodegradation of incretins such as glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. DPP4 inhibitors help to increase the postprandial insulin secretion and inhibit glucagon secretion through the inhibition of inactivation of glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide[1].

Diabetes is a group of metabolic disorders occurring due to the defects in insulin secretion and insulin action. It has been estimated that more than 500 million people around the globe were living with diabetes in 2018 and the numbers are increasing daily[2].

Inappropriate use of multiple medications or polypharmacy is more common among diabetic patients as they may receive many medications to manage comorbid conditions such as hypertension, dyslipidemia, other cardiovascular problems, infections, depression, and others along with their antidiabetic medications. The risk of drug interactions increases with the number of comedications. Drug interaction is defined as the interference of effects of adrug by the concomitantly administered other drug(s), herbs, minerals, vitamins, food, fruit juices, tobacco smoke or alcohol, and the drug interaction resulting in increased unintended effects or decreased intended effects is termed adverse drug interaction[3,4].

The cytochrome P450 (CYP) enzymes are involved in the phase 1 metabolism of drugs and they consist of 57 different CYP forms. Almost 90% of drugs are metabolized by seven CYP enzymes including CYP3A4 and others[5]. Saxagliptin is a substrate of CYP enzymes, and it is primarily metabolized by CYP3A4/5 to form the active metabolite, 5-hydroxy saxagliptin through hydroxylation[6]. Moreover, other DPP4 inhibitors such as sitagliptin[7], linagliptin[8], gemigliptin[9] and teneligliptin[10] are weak substrates of the CYP3A4 enzyme. They are metabolized incompletely by CYP3A4, and major parts of the drugs are excreted as unchanged drug through urine except linagliptin, which is excreted through feces. Vildagliptin[11] and anagliptin[12] are metabolized by cyano group hydrolysis and about 50% of the administered dose is excreted as unchanged drug. The drugs inhibiting or inducing the CYP3A4 enzyme may interact with DPP4 inhibitors as some of them are substrates of the CYP3A4 enzyme.

P-glycoprotein (P-gp) is an efflux transporter and it is also known as multidrug resistance protein 1 as it is overexpressed in tumor cells causing resistance to different anticancer drugs. P-gp is involved in the absorption and excretion of drugs as it is also found in various tissues like small intestine, liver and kidney. P-gp pumps the orally administered drugs back in to lumen and limit their bioavailability[13]. DPP4 inhibitors have been identified as substrates of P-gp[14] and the drugs inducing or inhibiting P-gp transporters may also affect the pharmacokinetics of DPP4 inhibitors.

**LITERATURE REVIEW**

As the DPP4 inhibitors are the substrates of both CYP3A4 enzymes and the P-gp transporter, the present review is focused on the possible drug-drug interactions of them. The literature review was done in databases such as MEDLINE/PubMed/PMC, ScienceDirect, Google scholar, Cochrane Library and reference lists using the keywords such as drug interactions, sitagliptin, saxagliptin, linagliptin, gemigliptin, teneligliptin, vildagliptin, anagliptin, CYP3A4 and P-gp efflux pump.

**LITERATURE REVIEW RESULTS**

Most of the drug-drug interactions of DPP4 inhibitors involve mainly saxagliptin as it is metabolized extensively by the CYP3A4 enzyme. The plasma concentrations of saxagliptin increased by the concomitant administration of CYP3A4 and P-gp inhibitors such as ketoconazole and diltiazem and future studies are required to confirm the possibility of drug-drug interactions with other CYP3A4 inhibitors. In addition, other DPP4 inhibitors such as sitagliptin, linagliptin, gemigliptin and teneligliptin interact with CYP3A4 inhibitors insignificantly as they are weak substrates of CYP3A4 enzyme. The prescribers and the pharmacists are required to be aware of the drug-drug interactions of saxagliptin to prevent adverse complications.

***Ketoconazole***

Ketoconazole is an antifungal agent and it is a known potent inhibitor of CYP3A4 enzyme and P-gp transporter[15]. It has been observed that the plasma exposure of saxagliptin was increased by the concurrent administration of ketoconazole due to the inhibition of CYP3A4 enzyme-mediated metabolism of saxagliptin and a weak inhibition of P-gp mediated transport. Hence, it has been suggested to use the lowest therapeutic dose (2.5 mg) of saxagliptin when concomitant use of ketoconazole and saxagliptin is necessary[16]. Significant elevation of plasma concentrations of gemigliptin was observed in healthy male Korean volunteers who took ketoconazole along with gemigliptin[17] while there was no significant interaction reported with the concomitant use of ketoconazole and teneligliptin[18].

***Diltiazem***

Diltiazem is a calcium channel blocker and it is indicated in the management of hypertension, angina and certain cardiac arrhythmias. Diltiazem is a moderate inhibitor of CYP3A4 enzyme and P-gp transporter[19] and its coadministration with saxagliptin resulted in a significant increase in plasma exposure of saxagliptin[16].

***Other CYP3A4 inhibitors***

The plasma concentrations of saxagliptin might be elevated by its coadministration with strong CYP3A4 inhibitors including macrolide antibiotics like clarithromycin and antiretroviral drugs (protease inhibitors) such as ritonavir, atazanavir, and others[20]. Future studies are required to confirm the interaction of macrolide antibiotics, antiretroviral drugs and other potent CYP3A4 inhibitors with saxagliptin and other DPP4 inhibitors.

***3-Hydroxy-3-Methyl-Glutaryl-CoA reductase inhibitors (statins)***

3-Hydroxy-3-Methyl-Glutaryl-CoA reductase inhibitors or statins are used to lower the risk of acute cardiovascular events by controlling dyslipidemia[21]. Statins include lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, pravastatin, rosuvastatin and pitavastatin[22].The statins such as lovastatin, simvastatin, atorvastatin and cerivastatin are reported to be substrates of CYP3A4 enzyme and P-gp transporter[23].

The exposure of saxagliptin was slightly increased by the concomitant use of simvastatin[16], and no clinically significant changes in pharmacokinetics of simvastatin and sitagliptin[24] or vildagliptin[25] was observed when they were used concomitantly.

Although the initiation of sitagliptin in a patient with chronic renal insufficiency and receiving simvastatin resulted in developing the symptoms of rhabdomyolysis such as leg pain, weakness and tenderness[26] the efficacy and safety of the fixed dose combination of sitagliptin and simvastatin was found to be acceptable[7]. However, the pharmacokinetics of either gemigliptin or rosuvastatin was not altered during their concurrent use[27].

Furthermore, it has been reported that a patient taking sitagliptin and lovastatin[28] and the patients taking sitagliptin and atorvastatin[29,30] developed rhabdomyolysis. The patients taking sitagliptin along with statins like atorvastatin and lovastatin are required to be monitored for the symptoms of muscle toxicity.

***Warfarin***

Warfarin is an oral anticoagulant agent, and R-warfarin is a substrate of CYP1A2 and CYP3A4 enzymes[31]. The pharmacokinetics of warfarin and sitagliptin[32], linagliptin[33], or vildagliptin[34] did not significantly get altered during their concomitant use, and it has been reported that no dosage adjustments of either drugs are required.

***Digoxin***

Digoxin is a cardio tonic agent, and it is approved to treat patients with heart failure and arrhythmias including atrial fibrillation[35]. Digoxin is a substrate of P-gp and its co-administration with linagliptin[36] or vildagliptin[37] did not lead to significant alterations in pharmacokinetic parameters of digoxin. Moreover, no dosage adjustment of either drugs are required when digoxin and linagliptin or vildagliptin are used concomitantly.

***Cyclosporine***

Cyclosporine is an immunosuppressant, and it is an inhibitor of CYP3A4 enzymes[38] and P-gp transporter[39]. The Pgp-mediated transport of sitagliptin was reported to be inhibited significantly by the coadministration of cyclosporine[40]. The magnitude of this interaction is considered low as sitagliptin has a high safety margin[41].

***Rifampicin***

Rifampicin is an anti‐tubercular antibiotic, and it is a potent inducer of CYP3A4 enzymes and P-gp transporter[42]. Clinically insignificant reduction of systemic exposure of saxagliptin was observed when it was coadministered with rifampicin and no dosage adjustment of saxagliptin is required[43].However, the concomitant use of gemigliptin and rifampicin in Korean volunteers resulted in significant reduction of systemic exposure of gemigliptin. The dose of gemigliptin may need to be adjusted when concurrent use is necessary[17].

**CONCLUSION**

Saxagliptin is a substrate of CYP3A4/5 enzymes and other DPP4 inhibitors such as sitagliptin, linagliptin, gemigliptin and teneligliptin are metabolized incompletely by CYP3A4 enzymes as they are weak substrates of CYP3A4. The plasma concentrations of saxagliptin have been reported to be increased significantly by the concomitant administration of ketoconazole or diltiazem while no significant interactions between various DPP4 inhibitors and drugs like warfarin, digoxin or cyclosporine have been identified.

**REFERENCES**

1 **Deacon CF**. Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. *Front Endocrinol (Lausanne)* 2019; **10**: 80 [PMID: 30828317 DOI: 10.3389/fendo.2019.00080]

2 **Kaiser AB**, Zhang N, Van Der Pluijm WO. Global Prevalence of Type 2 Diabetes over the Next Ten Years (2018-2028). *Diabetes* 2018; **67** (Supplement 1) [DOI: 10.2337/db18-202-LB]

3 **Mohamed N**, Maideen P. Thiazolidinediones and their Drug Interactions involving CYP enzymes. *A J Physiol Biochem Pharmacol* 2018; **8**: 47-54 [DOI: 10.5455/ajpbp.20181022083057]

4 Maideen NM. Tobacco smoking and its drug interactions with comedications involving CYP and UGT enzymes and nicotine. World J Pharmacol 2019; 8: 14-25 [DOI: 10.5497/wjp.v8.i2.14]

5 **Raunio H**, Kuusisto M, Juvonen RO, Pentikäinen OT. Modeling of interactions between xenobiotics and cytochrome P450 (CYP) enzymes. *Front Pharmacol* 2015; **6**: 123 [PMID: 26124721 DOI: 10.3389/fphar.2015.00123]

6 **Stoltze D**, Böttger E. [Computerized tomography and densitometry using computerized tomography in abdominal injuries]. *Zentralbl Chir* 1981; **106**: 400-407 [PMID: 7282159 DOI: 10.1007/s40262-016-0421-4]

7 **Ramadan WH**, Kabbara WK. Sitagliptin/Simvastatin: a first combination tablet to treat type 2 diabetes and hypercholesterolemia--a review of its characteristics. *Vasc Health Risk Manag* 2015; **11**: 125-132 [PMID: 25709467 DOI: 10.2147/VHRM.S79198]

8 **Ceriello A**, Inagaki N. Pharmacokinetic and pharmacodynamic evaluation of linagliptin for the treatment of type 2 diabetes mellitus, with consideration of Asian patient populations. *J Diabetes Investig* 2017; **8**: 19-28 [PMID: 27180612 DOI: 10.1111/jdi.12528]

9 **Kim N**, Patrick L, Mair S, Stevens L, Ford G, Birks V, Lee SH. Absorption, metabolism and excretion of [14C]gemigliptin, a novel dipeptidyl peptidase 4 inhibitor, in humans. *Xenobiotica* 2014; **44**: 522-530 [PMID: 24304170 DOI: 10.3109/00498254.2013.865856]

10 **Kishimoto M**. Teneligliptin: a DPP-4 inhibitor for the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes* 2013; **6**: 187-195 [PMID: 23671395 DOI: 10.2147/DMSO.S35682]

11 **He YL**. Clinical pharmacokinetics and pharmacodynamics of vildagliptin. *Clin Pharmacokinet* 2012; **51**: 147-162 [PMID: 22339447 DOI: 10.2165/11598080-000000000-00000]

12 **Furuta S**, Smart C, Hackett A, Benning R, Warrington S. Pharmacokinetics and metabolism of [14C]anagliptin, a novel dipeptidyl peptidase-4 inhibitor, in humans. *Xenobiotica* 2013; **43**: 432-442 [PMID: 23075005 DOI: 10.3109/00498254.2012.731618]

13 **Finch A**, Pillans P. P-glycoprotein and its role in drug-drug interactions. *Aust Prescr* 2014; **37**: 137-139 [DOI: 10.18773/austprescr.2014.050]

14 **Filippatos TD**, Athyros VG, Elisaf MS. The pharmacokinetic considerations and adverse effects of DPP-4 inhibitors [corrected]. *Expert Opin Drug Metab Toxicol* 2014; **10**: 787-812 [PMID: 24746233 DOI: 10.1517/17425255.2014.907274]

15 **Ramos L**, Brignol N, Bakhtiar R, Ray T, Mc Mahon LM, Tse FL. High-throughput approaches to the quantitative analysis of ketoconazole, a potent inhibitor of cytochrome P450 3A4, in human plasma. *Rapid Commun Mass Spectrom* 2000; **14**: 2282-2293 [PMID: 11114039 DOI: 10.1002/1097-0231(20001215)14:23<2282::AID-RCM164>3.0.CO;2-V]

16 **Patel CG**, Li L, Girgis S, Kornhauser DM, Frevert EU, Boulton DW. Two-way pharmacokinetic interaction studies between saxagliptin and cytochrome P450 substrates or inhibitors: simvastatin, diltiazem extended-release, and ketoconazole. *Clin Pharmacol* 2011; **3**: 13-25 [PMID: 22287853 DOI: 10.2147/CPAA.S15227]

17 **Noh YH**, Lim HS, Jin SJ, Kim MJ, Kim YH, Sung HR, Choi HY, Bae KS. Effects of ketoconazole and rifampicin on the pharmacokinetics of gemigliptin, a dipeptidyl peptidase-IV inhibitor: a crossover drug-drug interaction study in healthy male Korean volunteers. *Clin Ther* 2012; **34**: 1182-1194 [PMID: 22534255 DOI: 10.1016/j.clinthera.2012.04.001]

18 **Nakamaru Y**, Hayashi Y, Sekine M, Kinoshita S, Thompson J, Kawaguchi A, Davies M, Jürgen Heuer H, Yamazaki H, Akimoto K. Effect of ketoconazole on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor teneligliptin: an open-label study in healthy white subjects in Germany. *Clin Ther* 2014; **36**: 760-769 [PMID: 24726088 DOI: 10.1016/j.clinthera.2014.03.002]

19 **Teng R**, Butler K. Effect of the CYP3A inhibitors, diltiazem and ketoconazole, on ticagrelor pharmacokinetics in healthy volunteers. *J Drug Assess* 2013; **2**: 30-39 [PMID: 27536435 DOI: 10.3109/21556660.2013.785413]

20 **May M**, Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs. *Ther Adv Endocrinol Metab* 2016; **7**: 69-83 [PMID: 27092232 DOI: 10.1177/2042018816638050]

21 **Oliveira EF**, Santos-Martins D, Ribeiro AM, Brás NF, Cerqueira NS, Sousa SF, Ramos MJ, Fernandes PA. HMG-CoA Reductase inhibitors: an updated review of patents of novel compounds and formulations (2011-2015). *Expert Opin Ther Pat* 2016; **26**: 1257-1272 [PMID: 27537201 DOI: 10.1080/13543776.2016.1216977]

22 **Neuvonen PJ**. Drug interactions with HMG-CoA reductase inhibitors (statins): the importance of CYP enzymes, transporters and pharmacogenetics. *Curr Opin Investig Drugs* 2010; **11**: 323-332 [PMID: 20178046 DOI: 10.1016/j.cct.2010.01.003]

23 **Law M**, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006; **97**: 52C-60C [PMID: 16581329 DOI: 10.1016/j.amjcard.2005.12.010]

24 **Bergman AJ**, Cote J, Maes A, Zhao JJ, Roadcap BA, Sun L, Valesky RJ, Yang A, Keymeulen B, Mathijs Z, De Smet M, Laethem T, Davies MJ, Wagner JA, Herman GA. Effect of sitagliptin on the pharmacokinetics of simvastatin. *J Clin Pharmacol* 2009; **49**: 483-488 [PMID: 19204138 DOI: 10.1177/0091270008330983]

25 **Ayalasomayajula SP**, Dole K, He YL, Ligueros-Saylan M, Wang Y, Campestrini J, Humbert H, Sunkara G. Evaluation of the potential for steady-state pharmacokinetic interaction between vildagliptin and simvastatin in healthy subjects. *Curr Med Res Opin* 2007; **23**: 2913-2920 [PMID: 17931461 DOI: 10.1185/030079907X233296]

26 **Kao DP**, Kohrt HE, Kugler J. Renal failure and rhabdomyolysis associated with sitagliptin and simvastatin use. *Diabet Med* 2008; **25**: 1229-1230 [PMID: 19046202 DOI: 10.1111/j.1464-5491.2008.02536.x]

27 **Choi HY**, Lim HS, Kim YH, Jeon HS, Kim MJ, Lee SH, Jung JH, Lee YK, Kim HJ, Bae KS. Evaluation of the pharmacokinetics of the DPP-4 inhibitor gemigliptin when coadministered with rosuvastatin or irbesartan to healthy subjects. *Curr Med Res Opin* 2015; **31**: 229-241 [PMID: 25350224 DOI: 10.1185/03007995.2014.980886]

28 **DiGregorio RV**, Pasikhova Y. Rhabdomyolysis caused by a potential sitagliptin-lovastatin interaction. *Pharmacotherapy* 2009; **29**: 352-356 [PMID: 19249953 DOI: 10.1592/phco.29.3.352]

29 **Khan MW**, Kurian S, Bishnoi R. Acute-onset rhabdomyolysis secondary to sitagliptin and atorvastatin interaction. *Int J Gen Med* 2016; **9**: 103-106 [PMID: 27199569 DOI: 10.2147/IJGM.S98543]

30 **Bhome R**, Penn H. Rhabdomyolysis precipitated by a sitagliptin-atorvastatin drug interaction. *Diabet Med* 2012; **29**: 693-694 [PMID: 22023482 DOI: 10.1111/j.1464-5491.2011.03502.x]

31 **King CA**, Babcock KM, Godios RJ, King BS. Significant drug-drug interaction between warfarin and nafcillin. *Ther Adv Drug Saf* 2018; **9**: 667-671 [PMID: 30479741 DOI: 10.1177/2042098618796186]

32 **Wright DH**, Herman GA, Maes A, Liu Q, Johnson-Levonas AO, Wagner JA. Multiple doses of sitagliptin, a selective DPP-4 inhibitor, do not meaningfully alter pharmacokinetics and pharmacodynamics of warfarin. *J Clin Pharmacol* 2009; **49**: 1157-1167 [PMID: 19783710 DOI: 10.1177/0091270009341653]

33 **Graefe-Mody EU**, Brand T, Ring A, Withopf B, Stangier J, Iovino M, Woerle HJ. Effect of linagliptin on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *Int J Clin Pharmacol Ther* 2011; **49**: 300-310 [PMID: 21543033 DOI: 10.5414/CP201507]

34 **He YL**, Sabo R, Riviere GJ, Sunkara G, Leon S, Ligueros-Saylan M, Rosenberg M, Dole WP, Howard D. Effect of the novel oral dipeptidyl peptidase IV inhibitor vildagliptin on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Curr Med Res Opin* 2007; **23**: 1131-1138 [PMID: 17519080 DOI: 10.1185/030079907X188008]

35 **Cheng JW**, Rybak I. Use of digoxin for heart failure and atrial fibrillation in elderly patients. *Am J Geriatr Pharmacother* 2010; **8**: 419-427 [PMID: 21335295 DOI: 10.1016/j.amjopharm.2010.10.001]

36 **Friedrich C**, Ring A, Brand T, Sennewald R, Graefe-Mody EU, Woerle HJ. Evaluation of the pharmacokinetic interaction after multiple oral doses of linagliptin and digoxin in healthy volunteers. *Eur J Drug Metab Pharmacokinet* 2011; **36**: 17-24 [PMID: 21340661 DOI: 10.1007/s13318-011-0028-y]

37 **He YL**, Sabo R, Sunkara G, Bizot MN, Riviere GJ, Leon S, Ligueros-Saylan M, Dole WP, Howard D. Evaluation of pharmacokinetic interactions between vildagliptin and digoxin in healthy volunteers. *J Clin Pharmacol* 2007; **47**: 998-1004 [PMID: 17660482 DOI: 10.1177/0091270007301802]

38 **Pakkir Maideen NM**, Manavalan G, Balasubramanian K. Drug interactions of meglitinide antidiabetics involving CYP enzymes and OATP1B1 transporter. *Ther Adv Endocrinol Metab* 2018; **9**: 259-268 [PMID: 30181852 DOI: 10.1177/2042018818767220]

39 **Dorababu M**, Nishimura A, Prabha T, Naruhashi K, Sugioka N, Takada K, Shibata N. Effect of cyclosporine on drug transport and pharmacokinetics of nifedipine. *Biomed Pharmacother* 2009; **63**: 697-702 [PMID: 19819100 DOI: 10.1016/j.biopha.2009.04.031]

40 **Krishna R**, Bergman A, Larson P, Cote J, Lasseter K, Dilzer S, Wang A, Zeng W, Chen L, Wagner J, Herman G. Effect of a single cyclosporine dose on the single-dose pharmacokinetics of sitagliptin (MK-0431), a dipeptidyl peptidase-4 inhibitor, in healthy male subjects. *J Clin Pharmacol* 2007; **47**: 165-174 [PMID: 17244767 DOI: 10.1177/0091270006296523]

41 **Chu XY**, Bleasby K, Yabut J, Cai X, Chan GH, Hafey MJ, Xu S, Bergman AJ, Braun MP, Dean DC, Evers R. Transport of the dipeptidyl peptidase-4 inhibitor sitagliptin by human organic anion transporter 3, organic anion transporting polypeptide 4C1, and multidrug resistance P-glycoprotein. *J Pharmacol Exp Ther* 2007; **321**: 673-683 [PMID: 17314201 DOI: 10.1124/jpet.106.116517]

42 **Kim KA**, Park PW, Liu KH, Kim KB, Lee HJ, Shin JG, Park JY. Effect of rifampin, an inducer of CYP3A and P-glycoprotein, on the pharmacokinetics of risperidone. *J Clin Pharmacol* 2008; **48**: 66-72 [PMID: 18094221 DOI: 10.1177/0091270007309888]

43 **Upreti VV**, Boulton DW, Li L, Ching A, Su H, Lacreta FP, Patel CG. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of saxagliptin, a dipeptidyl peptidase-4 inhibitor, in healthy subjects. *Br J Clin Pharmacol* 2011; **72**: 92-102 [PMID: 21651615 DOI: 10.1111/j.1365-2125.2011.03937.x]

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