

Combined oral contraceptives as victims of drug interactions

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Supplemental Table 1. AUC geometric mean ratios and 90% confidence intervals of CYP3A substrates in the presence of CYP3A inducers shown in Figure 6.

CYP3A Probes	Corresponding COCs	CYP3A inducers	Classification	GMRs	90% CIs		References
Midazolam	DRSP/EE	Rifampin	strong	0.137	0.12	0.15	(Wiesinger et al., 2020)
Midazolam	LNG/EE	Rifampin	strong	0.137	0.14	0.15	(Wiesinger et al., 2020)
Quetiapine	LNG/EE	Phenytoin	strong	0.19	0.15	0.23	(Wong et al., 2001)
Midazolam	LNG/EE	Carbamazepine	strong	0.211	0.18 3	0.24	(Lutz et al., 2018)
Midazolam	LNG/EE	Carbamazepine	strong	0.211	0.18 3	0.24	(Lutz et al., 2018)
Midazolam	NET/EE	Carbamazepine	strong	0.211	0.18 3	0.24	(Lutz et al., 2018)
Midazolam	NET/EE	Rifampin	strong	0.137	0.12 4	0.15	(Wiesinger et al., 2020)
Midazolam	NET/EE	Rifampin	strong	0.137	0.12 4	0.15	(Wiesinger et al., 2020)
Midazolam	NET/EE	Rifampin	strong	0.137	0.12 4	0.15	(Wiesinger et al., 2020)
Simvastatin	NGM/EE	Efavirenz	moderate	0.42	0.32	0.61	(Gerber et al., 2005)
Simvastatin	LNG/EE	Efavirenz	moderate	0.42	0.32	0.61	(Gerber et al., 2005)

Simvastatin	LNG/EE	Eslicarbazepine	moderate	0.5	0.4	0.64	(Falcao et al., 2013)
Midazolam	NET/EE	Rifampin	moderate	0.24	0.22	0.27	(van Dyk et al., 2019)
Midazolam	NET/EE	St. John's wort	moderate	0.34	0.31	0.39	(Xie et al., 2005)
Midazolam	NET/EE	Rifabutin	moderate	0.31	0.27	0.35	(Lutz et al., 2018)
Midazolam	NET/EE	Rifabutin	moderate	0.31	0.27	0.35	(Lutz et al., 2018)
Sildenafil	NET/EE	Bosentan	moderate	0.37	0.32	0.43	(Burgess et al., 2008)
Sildenafil	NET/EE	Etravirine	moderate	0.43	0.36	0.51	(NDA022187, 2008)
Midazolam	NET/EE	Elagolix	moderate	0.46	0.41	0.5	(Polepally et al., 2020)
Itraconazole	NET/EE	Nevirapine	Weak/moderate	0.38 ¹	n/a	n/a	(Jaruratanasirikul and Sriwiriyan, 2007)
Indinavir	NET/EE	Nevirapine	Weak/moderate	0.69	0.61	0.78	(VIRAMUNE, 2022)
Midazolam	LNG/EE	Elagolix	Weak/Moderate	0.65	0.58	0.72	(Polepally et al., 2020)
Midazolam	LNG/EE	Elagolix	Weak/Moderate	0.46	0.41	0.5	(Polepally et al., 2020)
Midazolam	DRSP/EE	Rifampin	weak	0.54	0.49	0.59	(Polepally et al., 2020)
Midazolam	NGM/EE	Elagolix	weak	0.65	0.58	0.72	(Polepally et al., 2020)
Midazolam	LNG/EE	Rifampin	weak	0.54	0.49	0.59	(Wiesinger et al., 2020)
Midazolam	LNG/EE	Lersivirine	weak	0.64	0.52	0.77	(Davis et al., 2012)
Midazolam	NET/EE	Elagolix	weak	0.65	0.58	0.72	(Polepally et al., 2020)
Midazolam	NET/EE	Rifampin	weak	0.54	0.49	0.59	(Wiesinger et al., 2020)
Midazolam	NET/EE	St. John's wort	weak	0.65	0.49	0.81	(Hall et al., 2003)

¹Data presented as arithmetic mean ratio.

Abbreviations: AUC = area under the concentration-time curve; COCs = Combined oral contraceptives; CIs = confidence intervals; CYP = cytochrome P450; DRSP = drospirenone; EE = ethinyl estradiol; GMRs = geometric mean ratios; LNG = levonorgestrel; n/a = not available; NET = norethindrone; NGM = norgestimate

References:

- Burgess G, Hoogkamer H, Collings L, and Dingemans J (2008) Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. *Eur J Clin Pharmacol* **64**:43-50.
- Davis J, Langdon G, Layton G, Chong CL, Ndongo MN, and Vourvahis M (2012) The effect of lersivirine, a next-generation NNRTI, on the pharmacokinetics of midazolam and oral contraceptives in healthy subjects. *Eur J Clin Pharmacol* **68**:1567-1572.
- Falcao A, Pinto R, Nunes T, and Soares-da-Silva P (2013) Effect of repeated administration of eslicarbazepine acetate on the pharmacokinetics of simvastatin in healthy subjects. *Epilepsy Res* **106**:244-249.
- Gerber JG, Rosenkranz SL, Fichtenbaum CJ, Vega JM, Yang A, Alston BL, Brobst SW, Segal Y, Aberg JA, and Team ACTGA (2005) Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* **39**:307-312.
- Hall SD, Wang Z, Huang SM, Hamman MA, Vasavada N, Adigun AQ, Hilligoss JK, Miller M, and Gorski JC (2003) The interaction between St John's wort and an oral contraceptive. *Clin Pharmacol Ther* **74**:525-535.
- Jaruratanasirikul S and Sriwiriyan S (2007) Pharmacokinetic study of the interaction between itraconazole and nevirapine. *Eur J Clin Pharmacol* **63**:451-456.
- Lutz JD, Kirby BJ, Wang L, Song Q, Ling J, Massetto B, Worth A, Kearney BP, and Mathias A (2018) Cytochrome P450 3A Induction Predicts P-glycoprotein Induction; Part 2: Prediction of Decreased Substrate Exposure After Rifabutin or Carbamazepine. *Clin Pharmacol Ther* **104**:1191-1198.
- NDA021911 (2008) Drug approval package: BANZEL (clinical pharmacology biopharmaceutics review) <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021911Orig1s000ClinPharmR_P1.pdf>.
- NDA022187 (2008) Drug approval package: INTELENCE (clinical pharmacology biopharmaceutics review) <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022187s000_ClinPharmR_P1.pdf>.
- Polepally AR, Ng JW, Salem AH, Dufek MB, Parikh A, Carter DC, Kamradt K, Mostafa NM, and Shebley M (2020) Assessment of Clinical Drug-Drug Interactions of Elagolix, a Gonadotropin-Releasing Hormone Receptor Antagonist. *J Clin Pharmacol* **60**:1606-1616.
- Prueksaritanont T, Vega JM, Zhao J, Gagliano K, Kuznetsova O, Musser B, Amin RD, Liu L, Roadcap BA, Dilzer S, Lasseter KC, and Rogers JD (2001) Interactions between simvastatin and troglitazone or pioglitazone in healthy subjects. *J Clin Pharmacol* **41**:573-581.
- van Dyk M, Miners JO, Marshall JC, Wood LS, Hopkins A, Sorch MJ, and Rowland A (2019) Identification of the caffeine to trimethyluric acid ratio as a dietary biomarker to characterise variability in cytochrome P450 3A activity. *Eur J Clin Pharmacol* **75**:1211-1218.
- VIRAMUNE (2022) VIRAMUNE Prescribing Information <https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020636s052,020933s043lbl.pdf>.

- Wiesinger H, Klein S, Rottmann A, Nowotny B, Riecke K, Gashaw I, Brudny-Kloppel M, Fricke R, Hochel J, and Friedrich C (2020) The Effects of Weak and Strong CYP3A Induction by Rifampicin on the Pharmacokinetics of Five Progestins and Ethinylestradiol Compared to Midazolam. *Clin Pharmacol Ther* **108**:798-807.
- Wong YW, Yeh C, and Thyrum PT (2001) The effects of concomitant phenytoin administration on the steady-state pharmacokinetics of quetiapine. *J Clin Psychopharmacol* **21**:89-93.
- Xie RJ, Tan LH, Polasek EC, Hong C, Teillol-Foo M, Gordi T, Sharma A, Nickens DJ, Arakawa T, Knuth DW, and Antal EJ (2005) CYP3A and P-glycoprotein activity induction with St. John's Wort in healthy volunteers from 6 ethnic populations. *Journal of Clinical Pharmacology* **45**:352-356.
- Zaccara G, Gangemi PF, Bendoni L, Menge GP, Schwabe S, and Monza GC (1993) Influence of single and repeated doses of oxcarbazepine on the pharmacokinetic profile of felodipine. *Ther Drug Monit* **15**:39-42.