

Supplemental data for

Drug Metabolism and Disposition

Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A systematic review of published models, applications and model verification

Jennifer E. Sager, Jingjing Yu, Isabelle Ragueneau-Majlessi, Nina Isoherranen

Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, WA, USA (J.E.S., I.R., J.Y., N.I.)

Supplemental Table 1: Pharmaceutical agents classified as in vivo P450 substrates, inhibitors, and inducers in the FDA and EMA drug-interaction guidance

Enzyme	Sensitive Substrates	NTI ^a Substrates	Inhibitors	Inducers
CYP1A2	alosetron, caffeine* , duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline* , tizanidine	Strong: ciprofloxacin, enoxacin*, fluvoxamine Moderate: methoxsalen, mexiletine, phenylpropanolamine, thiabendazole, vemurafenib, zileuton Weak: acyclovir, allopurinol, caffeine, cimetidine, daidzein, disulfiram, famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil	Moderate: montelukast, phenytoin Weak: moricizine, omeprazole, phenobarbital,
CYP2B6	bupropion*, efavirenz*		Weak: clopidogrel, ticlopidine*, prasugrel	Moderate: efavirenz , rifampin Weak: nevirapine
CYP2C8	<i>amodiaquine</i> , repaglinide*	paclitaxel	Strong: gemfibrozil* Weak: fluvoxamine, ketoconazole, trimethoprim	Moderate: rifampin
CYP2C9	celecoxib	phenytoin , S- warfarin* , <i>tolbutamide</i>	Moderate: amiodarone , fluconazole*, miconazole, oxandrolone Weak: capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfapyrazone, tigecycline, voriconazole, zafirlukast	Moderate: carbamazepine, rifampin Weak: aprepitant, bosentan, phenobarbital
CYP2C19	clobazam , lansoprazole, omeprazole* , S-mephenytoin	S-mephenytoin	Strong: fluconazole, fluvoxamine, ticlopidine Moderate: esomeprazole , fluoxetine, moclobemide, omeprazole*, voriconazole Weak: armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole	Moderate: rifampin Weak: artemisinin
CYP2D6	atomoxetine, desipramine*, dextromethorphan , metoprolol* , nebivolol, perphenazine, tolterodine, venlafaxine	thioridazine, pimozone	Strong: bupropion, fluoxetine* , paroxetine* , quinidine* Moderate: cinacalcet, duloxetine, terbinafine Weak: amiodarone, celecoxib, clobazam, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, pazopanib, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil, vemurafenib	not known

<p>CYP3A4</p>	<p>alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam*, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil</p>	<p>alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine</p>	<p>Strong: boceprevir, clarithromycin*, conivaptan, indinavir, itraconazole*, ketoconazole*, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir*, saquinavir, telaprevir, telithromycin, voriconazole</p> <p>Moderate: amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil</p> <p>Weak: alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, goldenseal, isoniazid, lapatinib, nilotinib, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton</p>	<p>Strong: avasimibe, carbamazepine, phenytoin, rifampin,</p> <p>Moderate: bosentan, efavirenz, etravirine, modafinil, nafcillin</p> <p>Weak: amprenavir, aprepitant, armodafinil, pioglitazone, prednisone, rufinamide, vemurafenib</p>
----------------------	--	--	--	---

^a NTI= Narrow Therapeutic Index. Drugs in bold are listed in Tables 3-7. Drugs in italic are listed only in EMA guidance. * indicates that drugs are listed in both guidance.

Supplemental Table 2: In vivo substrates, inhibitors, and inducers for selected transporters from the FDA and EMA drug-interaction guidance

Transporters	Substrates	Inhibitors	Inducers
P-gp	aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil	avasimibe, carbamazepine, phenytoin, rifampin , St John's wort, tipranavir/ritonavir
BCRP	methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin , sulfasalazine, topotecan	cyclosporine , elacridar (GF120918), eltrombopag, gefitinib	not known
OATP1B1	atrasentan, atorvastatin , bosentan , ezetimibe, fluvastatin , glyburide , SN-38 (active metabolite of irinotecan), rosuvastatin , simvastatin acid, pitavastatin, pravastatin , repaglinide , rifampin, valsartan, olmesartan	atazanavir, cyclosporine , eltrombopag, gemfibrozil , lopinavir, rifampin, ritonavir, saquinavir, tipranavir	not known
OATP1B3	atorvastatin, rosuvastatin , pitavastatin, telmisartan, valsartan, olmesartan	atazanavir, cyclosporine , lopinavir, rifampin, ritonavir, saquinavir	not known
OCT2	amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin	cimetidine, quinidine	not known
OAT1	adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine	probenecid	not known
OAT3	acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin , rosuvastatin, sitagliptin	probenecid cimetidine, diclofenac	not known

Drugs in bold are listed in Tables 3-7. Drugs in italic are listed only in EMA guidance. * indicates that drugs are listed in both guidance.