

Inter-assay variation of the bile salt export protein activity assay.

N = 3-4 separate experiments.

DRUG	MEAN	Standard Deviation	% Coefficient of Variation
Cyclosporine A	0.4	0.3	66.1
Glyburide	2.5	1.2	47.7
Ketoconazole	4.2	2.2	53.5
Rifamycin SV	9.5	2.6	27.9
Nefazodone	7.0	3.2	45.2
Trazodone	90.0	17.3	19.2
Buspirone	>100	0.0	ND
Allopurinol	>100	0.0	ND

Supplemental Table 2 (Primary Data)

Drug Name (LTKB)	DILI Concern Category	DILI Label Sections	BSEP IC50 (μM)	Source	Mitotox IC ₅₀ (nmol/mg)*	Human Cmax (μM, total)†
albuterol	No-DILI-concern	No mention	>1000	(1)	NE	0.0580
beclomethasone	No-DILI-concern	No mention	10.3		NE	0.0002
betaine	No-DILI-concern	No mention	>1000	(2)	NE	599.0000
brompheniramine	No-DILI-concern	No mention	>100		NE	0.0360
clobetasol propionate	No-DILI-concern	No mention	8.5	(2)	NE	0.043
dobutamine	No-DILI-concern	No mention	>100		NE	1.3370
econazole	No-DILI-concern	No mention	13.4		>100	0.001
finasteride	No-DILI-concern	No mention	28.2	(3)	NE	0.0990
flumazenil	No-DILI-concern	No mention	>100		NE	1.1200
folic acid	No-DILI-concern	No mention	>1000	(1)	NE	0.1350
lithyronine	No-DILI-concern	No mention	11.27	(1)	NE	0.1080
loperamide	No-DILI-concern	No mention	67		NE	0.0080
midazolam	No-DILI-concern	No mention	41.7	(3)	NE	0.6500
mometasone	No-DILI-concern	No mention	9.3		NE	0.0003
nimodipine	No-DILI-concern	No mention	10.1		>100	0.1950
oxybutynin	No-DILI-concern	No mention	27.4	(3)	NE	0.0220
phenoxybenzamine	No-DILI-concern	No mention	>100		NE	0.1970
phentolamine	No-DILI-concern	No mention	>1000	(1)	NE	0.0860
streptomycin	No-DILI-concern	No mention	>1000	(2)	NE	64.5400
sulfapyrazole	No-DILI-concern	No mention	11		NE	44.2500
(iso)retinoin	Less-DILI-concern	Warnings and Precautions	37.1	(4)	49.4	2.8700
amprenavir	Less-DILI-concern	Warnings and Precautions	44.8	(4)	NE	15.1500
buspirone	Less-DILI-concern	Adverse Reactions	>100		NE	0.0050
chenodiol	Less-DILI-concern	Warnings and Precautions	10.6		NE	8.0000
clofazimine	Less-DILI-concern	Adverse Reactions	12.9	(3)	NE	1.4800
clotrimazole	Less-DILI-concern	Warnings and Precautions	<10	(1)	>100	0.0870

cyclosporine	Less-DILI-concern	Warnings and Precautions	0.4		>100	0.7700
ethynodiol diacetate	Less-DILI-concern	Warnings and Precautions	62		20	0.0290
fenofibrate	Less-DILI-concern	Warnings and Precautions	41		NE	12.1390
fluvastatin	Less-DILI-concern	Warnings and Precautions	36.1	(3)	NE	0.6630
furosemide	Less-DILI-concern	Adverse Reactions	>1000	(2)	NE	18.1000
gefitinib	Less-DILI-concern	Warnings and Precautions	10.9	(3)	NE	0.3560
glimepiride	Less-DILI-concern	Adverse Reactions	34		NE	1.1230
glyburide	Less-DILI-concern	Adverse Reactions	1.5		14.24	0.2100
irbesartan	Less-DILI-concern	Adverse Reactions	7.31	(4)	NE	3.5050
losartan	Less-DILI-concern	Adverse Reactions	8.53	(4)	NE	0.6510
lovastatin	Less-DILI-concern	Warnings and Precautions	19.3	(4)	NE	0.0250
nelfinavir	Less-DILI-concern	Adverse Reactions	11.8	(4)	>100	7.0400
nicardipine	Less-DILI-concern	Adverse Reactions	7.9	(3)	>100	0.0810
nifedipine	Less-DILI-concern	Warnings and Precautions	69		NE	0.2710
nisoldipine	Less-DILI-concern	Adverse Reactions	33	(4)	NE	0.0129
pioglitazone	Less-DILI-concern	Warnings and Precautions	0.4	(3)	>100	2.9460
rifabutin	Less-DILI-concern	Adverse Reactions	26.7	(3)	NE	0.6849
saquinavir	Less-DILI-concern	Warnings and Precautions	2.9		NE	3.3600
simvastatin	Less-DILI-concern	Warnings and Precautions	24.7	(3)	>100	0.0240
telmisartan	Less-DILI-concern	Adverse Reactions	16.2	(3)	70.5	0.8510
trazodone	Less-DILI-concern	Adverse Reactions	90		NE	5.0600
trifluoperazine	Less-DILI-concern	Warnings and Precautions	<10	(1)	NE	0.0053
alpidem	Most-DILI-concern	Withdrawn	9.2	(2)	>100	0.2850
benzbromarone	Most-DILI-concern	Withdrawn	15.9		>100	4.3390
bicalutamide	Most-DILI-concern	Warnings and Precautions	29.3		48.9	1.9700
bosentan	Most-DILI-concern	Boxed Warning	29		>100	7.4330
danazol	Most-DILI-concern	Boxed Warning	18.7	(4)	87.5	0.7500
diclofenac	Most-DILI-concern	Warnings and Precautions	44		>100	7.9930
erythromycin estolate	Most-DILI-concern	Warnings and Precautions	13	(3)	65.8	4.1960
flutamide	Most-DILI-concern	Boxed Warning	68		57.6	0.3620

imatinib	Most-DILI-concern	Warnings and Precautions	25.1	(3)	NE	7.0900
indinavir	Most-DILI-concern	Warnings and Precautions	21.2	(3)	NE	11.7300
ketoconazole	Most-DILI-concern	Boxed Warning	3.4	(3)	80.6	12.5070
lapatinib	Most-DILI-concern	Boxed Warning	6.5	(3)	NE	4.1800
mefenamic acid	Most-DILI-concern	Warnings and Precautions	57		>100	26.9390
nefazodone	Most-DILI-concern	Boxed Warning	7		31.97	6.8000
paclitaxel	Most-DILI-concern	Adverse Reactions	15	(3)	NE	4.2700
progesterone	Most-DILI-concern	Adverse Reactions	<10	(1)	>100	0.1930
rifampicin	Most-DILI-concern	Warnings and Precautions	18.7		NE	8.5000
rifamycin sv	Most-DILI-concern	Warnings and Precautions	9.5		NE	2.7800
ritonavir	Most-DILI-concern	Warnings and Precautions	2.2	(3)	NE	19.6900
rosiglitazone	Most-DILI-concern	Adverse Reactions	3.75	(3)	>100	1.0440
sorafenib	Most-DILI-concern	Adverse Reactions	8	(3)	18.39	0.1320
telithromycin	Most-DILI-concern	Warnings and Precautions	30		NE	2.7700
trogglitazone	Most-DILI-concern	Withdrawn	5.9	(3)	53.2	6.3870
zafirlukast	Most-DILI-concern	Warnings and Precautions	11.1	(4)	66.2	1.2110

· *To convert to μM , divide IC_{50} value in nmol/mg mitochondrial protein by 4 (e.g. 100 nmol/mg = 25 μM).

· †Human C_{max} was obtained from Xu *et al.* (5) or other literature sources.

1. Warner DJ, Chen H, Cantin L-D, Kenna JG, Stahl S, Walker CL, et al. Mitigating the Inhibition of Human Bile Salt Export Pump by Drugs: Opportunities Provided by Physicochemical Property Modulation, In Silico Modeling, and Structural Modification. *Drug Metabolism and Disposition* 2012;40:2332-2341.
2. Dawson S, Stahl S, Paul N, Barber J, Kenna JG. In vitro inhibition of the bile salt export pump correlates with risk of cholestatic drug-induced liver injury in humans. *Drug Metab Dispos* 2012;40:130-138.
3. Morgan RE, Trauner M, van Staden CJ, Lee PH, Ramachandran B, Eschenberg M, et al. Interference with bile salt export pump function is a susceptibility factor for human liver injury in drug development. *Toxicol Sci* 2010;118:485-500.
4. Morgan RE, van Staden CJ, Chen Y, Kalyanaraman N, Kalanzi J, Dunn RT, et al. A Multifactorial Approach to Hepatobiliary Transporter Assessment Enables Improved Therapeutic Compound Development. *Toxicological Sciences* 2013;136:216-241.
5. Xu JJ, Henstock PV, Dunn MC, Smith AR, Chabot JR, de Graaf D. Cellular imaging predictions of clinical drug-induced liver injury. *Toxicol Sci* 2008;105:97-105.