pharmaceutics

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Supplementary

Pharmacokinetics, Pharmacodynamics and Drug-Drug Interactions of New Anti-Migraine Drugs–Lasmiditan, Gepants, and Calcitonin-Gene-Related Peptide (CGRP) Receptor Monoclonal Antibodies

Danuta Szkutnik-Fiedler

Table S1. Possible drug-drug interactions of lasmiditan [14,28,31,35–38,40,42,45–47].

The risk or severity of serotonin syndrome can be potentially increased when lasmiditan is combined with the following drugs[1,♣]	Serum concentration of the following drugs (P-gp and/or BCRP substrates) may potentially increase when combined with lasmiditan[2,♣]	Serum concentration of lasmiditan (P-gp substrate) may potentially increase when it is combined with the following drugs[3,♣]	Lasmiditan may increase the bradycardic effects of the following drugs[♣]
5-hydroxytryptophan*	afatinib		acebutolol
alfentanil*	alpelisib		amlodipine
almotriptan*	ambrisentan		atenolol
amitriptiline*	apixaban		betaxolol
amoxapine*	belinostat		carteolol
buspirone*	bisoprolol		carvedilol
citalopram*	brentuximab vedotin		diltiazem
clomipramine*	cabazitaxel		esmolol
cyclobenzaprine*	ceritinib		felodipine
desipramine*	cladribine		isradipine
desvenlavaxine*	cobimetinib	clobazam	ivabradine
dexfenfluramine*	colchicine*	daclatasvir	labetalol
dextromethorphan*	cyclosporine	erythromycin	levobetaxolol
dihydroergotamine*	daunorubicin	fexofenadine	levobunolol
dolasetron*	delafloxacin	lapatinib	methyldopa
doxepin*	digitoxin	ritonavir	metipranolol
doxepin topical*	digoxin		metoprolol
duloxetine*	donepezil		nadolol
eletriptan*	doxorubicin		nebivolol
ergotamine*	edoxaban*		nicardipine
escitalopram*	etoposide		nifedipine
fenfluramine*	everolimus		nimodipine
fentanyl*	idelalisib		nisoldipine
fluoxetine*	imatinib		propranolol
fluvoxamine*	indacaterol		rivastigmine
frovatriptan*#	irinotecan		siponimod
furazolidone*	lemborexant		timolol

granisetron*	linagliptin
imipramine*	lusutrombopag
isocarboxazid*	methotrexate
levomilnacipran*	mibefradil
linezolid*	mirabegron
lorcaserin*	mitoxantrone
maprotiline*	nilotinib
meperidine*	nintedanib
methylene blue*	osimertinib
milnacipran*	ozanimod*
mirtazapine*	posaconazole
naratriptan*#	prucalopride
nefazodone*	quinidine
nortriptyline*	ranolazine
ondansetron*	rifaximin
palonosetron*	rimegepant
paroxetine*	riociguat
pentazocine*	rosuvastatin
phenelzine*	saquinavir
procarbazine*	selexipag
protriptyline*	sofosbuvir
rasagiline*	sulfasalazine
remifentanil*	tenofovir
rizatriptan*#	tenofovir alafenamide
safinamide*	tenofovir disoproxil
selegiline*	teriflunomide
sertraline*	topotecan
sibutramine*	vemurafenib
St. John's wort*	vinblastine
sufentanil*	vincristine
tapentadol*	
tranylcypromine*	
trazodone*	
trimipramine*	
tryptophan*	
venlafaxine*	
vilazodone*	
vortioxetine*	
zolmitriptan*#	

* Major interaction according to the www.drugs.com [46]; ♣ Information about the interaction can be found on both www.drugs.com [46] and www.drugbank.com [45]; [1] Lasmiditan is a direct serotonin receptor agonist. When administered concomitantly with other drugs that also increase 5-HT levels the risk of serotonin syndrome increases [14,28,31,35–38]. No clinical DDI studies were conducted to evaluate the clinical significance of these drug-drug interactions, except sumatriptan; # Coadministration of lasmiditan and sumatriptan did not cause serotonin syndrome or any clinically relevant interaction between these two drugs [40]; [2] Lasmiditan exhibited *in vitro* inhibition of intestinal P-gp and BCRP with drug-drug interaction indices I_{gut}/IC_{50} exceeded the FDA [47] cutoff value of 10, indicating that lasmiditan has the potential to inhibit P-gp or BCRP *in vivo* [42]. No clinical DDI studies were conducted; [3] Lasmiditan is a substrate for P-gp *in vitro*; therefore, combined administration of lasmiditan with P-gp inhibitors may result in a potential increase of its blood

concentration [14,21,28,35,42]. Lasmiditan, however, is a BCS Class I drug and is unlikely to be affected by P-gp inhibitors [42]. No clinical DDI studies were conducted.

Table S2. Possible drug-drug interactions of ubrogepant [45,46,53–55,57–59,63,65–67].

Serum concentration of ubrogepant may potentially increase when it is combined with the following drugs (BCRP and/or P-gp inhibitors)[1,♣]	Serum concentration of ubrogepant may potentially increase when it is combined with the following drugs (CYP3A4 inhibitors)[2,♣]	Serum concentration of ubrogepant may potentially decrease when it is combined with the following drugs (CYP3A4 inducers)[2,♣]
afatinib	abametapir topical	aminogluthethimide
bepridil	abiraterone	amobarbital
capmatinib	amiodarone	apalutamide*
carvedilol	amlodipine	armodafinil
curcumin	amprenavir	bexarotene
cyclosporine	aprepitant	bosentan
daclatasvir	atazanavir*	brigatinib
eliglustat	bicalutamide	butabarbital
eltrombopaq	boceprevir*	butalbital
eluxadoline	ceritinib*	carbamazepine*
encorafenib	chloramphenicol	cenobamate
flibanserin	cimetidine	dabrafenib
fostamatinib	ciprofloxacin	dexamethasone
fostemsavir	clarithromycin*	doravirine
gefitinib	clotrimazole	efavirenz
ibrutinib	cobicistat*	elagolix
lapatinib	conovaptan	enzalutamide*
lasmiditan	crizotinib	eslicarbazepine
midostaurin	danazol	etravirine
neratinib	darunavir	felbamate
niraparib	delavirdine*	fosphenytoin*
olaparib	diltiazem	glycerol phenylbutyrate
osimertinib	duvelisib	griseofulvin
ponatinib	erythromycin	ivosidenib
progesterone	fedratinib	lesinurad
propafenone	fluconazole	lorlatinib
quinidine	fluvoxamine	mephobarbital
quinine	fosamprenavir	metreleptin
regorafenib	fosaprepitant	mitotane*
rolapitant	goldenseal	modafinil
safinamide	grepafloxacin	nafcillin
sarecycline	idelalisib*	nevirapine
simeprevir	imatinib	oritavancin
sonidegib	indinavir*	oxcarbazepine
spironolactone	isavuconazonium	pentobarbital
tacrolimus	isoniazid	pexidartinib
tamoxifen	itraconazole*	phenobarbital*

tedizolid	ivacaftor	phenytoin*
teriflunomide	ketoconazole*	pitolisant
ticagrelor	lefamulin	primidone*
tolvaptan	lemborexant	rifabutin*
ulipristal	letermovir	rifampin*
uridine	levamlodipine	rifapentine*
valbenazine	lomitapide	rufinamide
venetoclax	mibefradil*	secobarbital
	mifepristone*	somapacitan-beco
	nefazodone*	somatrem
	nelfinavir*	somatropin
	nifedipine	St. John's wort*
	nilotinib	tazemetostat
	palbocilib	telotristat
	pazopanib	troglitazone
	posaconazole*	vemurafenib
	ranolazine	
	ribocilib	
	ritonavir*	
	rucaparib	
	saquinavir*	
	selpercatinib	
	stiripentol	
	suvorexant	
	telaprevir*	
	telithromycin*	
	troleandomycin*	
	tucatinib	
	verapamil	
	voriconazole*	
	voxelotor	
	zafirlukast	

* Major interaction according to the www.drugs.com [46] (strong CYP3A4 inhibitors or strong CYP3A4 inducers); * Major interaction according to the www.drugs.com [46] (strong CYP3A4 inhibitors or strong CYP3A4 inducers); ♣ Information about the interaction can be found on both www.drugs.com [46] and www.drugbank.com [45]; [1] No clinical DDI studies with inhibitors of P-gp and BCRP transporters have been performed [53,63]; [2] DDI studies with CYP3A4 modulators were conducted for verapamil, ketoconazole, and rifampin [63].

Recommended dosage:

i. BCRP and/or P-gp inhibitors: an initial ubrogepant dose is 50 mg, a second 50 mg dose may be administered at least 2 hours after the initial dose;
ii. strong CYP3A4 inhibitors: combinations should be avoided;
iii. moderate or weak CYP3A4 inhibitors: an initial ubrogepant dose is 50 mg, a second 50 mg dose should be avoided within 24 hours of the initial dose (moderate CYP3A4 inhibitors), a second 50 mg dose may be administered at least 2 hours after the initial dose (weak CYP3A4 inhibitors);
iv. strong CYP3A4 inducers: combinations should be avoided;

v. moderate or weak CYP3A4 inducers: an initial ubrogepant dose is 100, a second 100 mg dose may be administered at least 2 hours after the initial dose.

Table S3. Possible drug-drug interactions of rimegepant [45,46,69,71–73,76–78,80,82].

Serum concentration of rimegepant may potentially increase when it is combined with the following drugs (BCRP and/or P-gp inhibitors)[1,♣]	Serum concentration of rimegepant may potentially increase when it is combined with the following drugs (CYP3A4 inhibitors)[2,♣]	Serum concentration of rimegepant may potentially decrease when it is combined with the following drugs (CYP3A4 inducers)[2,♣]
afatinib amiodarone capmatinib cobimetinib cyclosporine eltrombopaq encorafenib fostemsavir gefitinib ibrutinib istradefylline lapatinib lasmiditan midostaurin neratinib niraparib olaparib osimertinib ponatinib propafenone regorafenib rolapitant safinamide sarecycline sonidegib sulfasalazine tacrolimus tafamidis tedizolid teriflunomide	abametapir topical abiraterone amprenavir aprepitant atazanavir* boceprevir* ceritinib* chloramphenicol ciprofloxacin clarithromycin* cobicistat* conovaptan crizotinib darunavir delavirdine* diltiazem dronedarone duvelisib erythromycin fedratinib fluconazole fosamprenavir fosaprepitant idelalisib* imatinib indinavir* isavuconazonium itraconazole* ivacaftor ketoconazole* letermovir mibefradil* nefazodone* nelfinavir* palbocilib posaconazole* ranolazine ribocilib ritonavir*	apalutamide* bosentan* carbamazepine* cenobamate* dabrafenib* dexamethasone* efavirenz* enzalutamide* eslicarbazepine* etravirine* fosphenytoin* lorlatinib* mitotane* modafinil* nafcillin* nevirapine* pexidartinib* phenobarbital* phenytoin* primidone* rifabutin* rifampin* rifapentine* somapacitan-beco somatrem St. John's wort* telotristat* vemurafenib

rucaparib
saquinavir*
selpercatinib
stiripentol
telaprevir*
telithromycin*
troleandomycin*
tucatinib
verapamil
voriconazole*
voxelotor

* Major interaction according to the www.drugs.com [46] (strong CYP3A4 inhibitors or strong CYP3A4 inducers); ♣ Information about the interaction can be found on both www.drugs.com [46] and www.drugbank.com [45]; [1] No clinical DDI studies with inhibitors of P-gp and BCRP transporters have been performed [80]; [2] DDI studies with CYP3A4 modulators were conducted for itraconazole and rifampin [80].

Recommended dosage:

i. BCRP and/or P-gp inhibitors: an initial rimegepant dose is 50 mg, a second 50 mg dose may be administered at least 2 hours after the initial dose;
ii. strong CYP3A4 inhibitors: combinations should be avoided;
iii. moderate CYP3A4 inhibitors: an initial rimegepant dose is 50 mg, a second 50 mg dose should be avoided within 24 hours of the initial dose;
iv. weak CYP3A4 inhibitors: an initial rimegepant dose is 50 mg, a second 50 mg dose may be administered at least 2 hours after the initial dose;
v. strong or moderate CYP3A4 inducers: combinations should be avoided;
vi. weak CYP3A4 inducers: an initial rimegepant dose is 100, a second 100 mg dose may be administered at least 2 hours after the initial dose.