הצעות לשימוש מושכל ב-PAXLOVID בחולה מטופל בתרופות כרוניות
גרסה 8 (13/7/2022)

הקדמה

- הטיפול ב-PAXLOVID מסייע במניעת מחלה קשה בחולי קורונה סימפטומטיים, כאשר ניתן תוך 3-5 ימים מתחילת הסימפטומים.
- טיפול זה מורכב עקב אינטראקציות בינו לבין תרופות רבות.
- טבלאות אלה נוצרו על מנת לסייע לרופא המטפל להחליט האם המטופל מתאים לטיפול ב-PAXLOVID (מבחינת אינטראקציות), ובאילו תנאים.
- ההמלצות נכתבו על בסיס עיון במקורות מידע זמינים כגון העלון לרופא, מיקרומדקס, UpToDate ומעיון בספרות אם נמצאה כזו רלבנטית. המלצה יכולה להיות אחת מהבאות:
  - לא לתת טיפול ב-PAXLOVID עקב אינטראקציה משמעותית ומסוכנת. (פה המקום לשקול טיפול חלופי כגון REMDESIVIR או MOLNUPIRAVIR).
  - לתת PAXLOVID ולהמשיך טיפול תרופתי כרוני ללא שינוי – אולי תוך מעקב אחר תופעות לוואי ספציפיות.
  - לתת PAXLOVID ולהפחית מינון טיפול כרוני במהלך הטיפול ב-PAXLOVID.
  - לתת PAXLOVID ולהפסיק טיפול תרופתי כרוני בזמן הטיפול ב-PAXLOVID בהתבסס על זמן מחצית החיים של התרופה המופסקת, התועלת שבטיפול והסיכון בהפסקה זמנית של הטיפול. כל הנ"ל תלויים בשיקול דעתו של הרופא לגבי הסיכון בהפסקת הטיפול:
    - לדוגמא - אם לחץ הדם גבוה מאד וקשה לאיזון (תחת הטיפול התרופתי) אז המלצה להפסיק טיפול ב-LERCANIDIPINE למשל אולי לא מתאימה לחולה, ואילו בחולה מאוזן סביב 120/80 שמעולם לא היו לו לחצי דם מאד מאד גבוהים, ניתן לשקול הפסקה זמנית של הטיפול.
    - לדוגמא - בחולה שמטופל באנטיקואגולציה עקב פרפור פרוזדורים עם CHADSVASC 2 נוכל להפסיק אנטיקואגולציה במהלך טיפול ב-PAXLOVID ואילו חולה עם פרפור פרוזדורים, CHADSVASC 6 עם אירועים מוחיים חוזרים, אולי עדיף לעבור ל-ENOXAPARIN במהלך הטיפול ב-PAXLOVID.
    - לדוגמא - בחולה שעשה בעבר אצירת שתן על רקע הגדלת פרוסטטה לא נוכל להפסיק טיפול תרופתי אך בחולה שסבל מתלונות קלות של פרוסטטיזם ומאוזן תחת טיפול, נוכל לשקול להפסיק טיפול זה זמנית על מנת לאפשר טיפול ב-PAXLOVID.
- רשימה זו התבססה תחילה על העלון האמריקאי והאירופאי לרופא של PAXLOVID וגדלה בעקבות המלצות ושאלות שהתקבלו. השינויים בגרסה זו לעומת הגרסה הקודמת מסומנים בצהוב ומתבססים על שינויים בעלון האמריקאי לרופא שעודכן ב-28/6/2022 ומידע נוסף שהצטבר.
- טבלה זו מכילה תרופות שקיימות בארץ ואינה מכילה את כלל האינטראקציות עם PAXLOVID. במידה וחולה נוטל תרופה ש**אינה** רשומה בטבלה זו, יש לברר באופן פרטני אינטראקציות עם PAXLOVID.

השינויים מגרסה 6 ו-7 כוללים:

- בטבלת התוויות הנגד:
  - הוספה התייחסות ל-Ivabradine (Coralan®) ו-Lumacaftor/Ivacaftor (Orkambi®)
- בטבלת ההמלצות לשימוש מושכל:
  - שינוי המלצה לגבי טיפול כרוני ב-Dabigatran (Pradaxa®)
  - הוספת התייחסות למספר תרופות לטיפול במיגרנות
  - הוספת התייחסות ל-Eplerenone (Inspra®)
  - הוספת התייחסות לתרופות לטיפול ב-Cystic Fibrosis (תיקון המלצות להפחתת מינון שפורסמו בגרסה 7)

במידה ויש הערות או הצעות נוספות ניתן ליצור קשר איתי:

ד"ר לי גולדשטיין יו"ר האיגוד הישראלי לפרקמקולוגיה קלינית Goldstein_le@clalit.org.il 050-6787786

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Do Not Use Paxlovid

Drug Class	Drug	Effect on conc.	Clinical effect	$t_{1/2}$	Comments	Recommendation
Anti-arrhythmic	Flecainide (Tambocor)	up		12-27 hours	Arrhythmias as of 2nd-3rd day	**Do not use PAX**
	Propafenone (Profex, Rythmex)	up		5-8 hours	Arrhythmias as of 2nd day	**Do not use PAX**
	Disopyramide (Rythmical)	up		10 hours		**Do not use PAX**
Anti-cancer	Apalutamide (Erleada)	-	Decreased PAX	3 days		**Do not use PAX**
	Ivosidenib	up	QTc prolongation Nephrotoxicity	58-129 hours		**Do not use PAX**
	Vincristine (Vincristine Teva)	up	Neuromuscular, GI toxicity Myelosuppression	85 hours		**Do not use PAX**
Anti-epilepsy	Carbamazepine Phenobarbital Phenytoin Primidone	-	Decreased PAX Increased anti-epileptic agents	15 hours 80 hours 22 hours	CYP34 inducers	**Do not use PAX**
Anti-fungal	Ketoconazole	up	Prolonged QT	8 hours	AUC X 3.4 **If impossible to stop ketoconazole, do not use PAX**	• **Stop ketoconazole** • Start PAX 24 hours later • Restart ketoconazole 24 hours after last dose PAX
	Isavuconazole	up	Ritonavir down	130 hours		**Do not use PAX**
Anti-infective	Rifampin	-	Decreased PAX	2-3 hours		**Do not use PAX**
Antipsychotics	Clozapine	up	QT prolongation	12 hours	Withdrawal effects if stopped abruptly	**Do not use PAX**
	Quetiapine	up	QT prolongation	6 hours	Withdrawal effects if stopped abruptly	**Do not use PAX**
	Pimozide (Orap)	up	QT prolongation	55 hours		**Do not use PAX**
	Lurasidone	up		18-40 hours		**Do not use PAX**

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Drug Class	Drug	Effect on conc.	Clinical effect	$t_{1/2}$	Comments	Recommendation
Cardiovascular agents	Ivabradine	up	Bradycardia or conduction disturbances	11 hours		**Do not use PAX**
Cystic fibrosis transmembrane conductance regulator potentiators	Lumacaftor / ivacaftor (Orkambi)	-	Decreased PAX	26 hours / 9 hours	• Lumacaftor is a strong inducer of CYP3A • Ivacaftor is a substrate of CYP3A4	**Do not use PAX**
HCV antivirals	Glecaprevir/ Pibrentasvir (Maviret)	up	Antiviral elevation	7 / 25 hours		**Do not use PAX**
Immuno-suppressant	Cyclosporine	up		19 hours	Elevated level of immuno-suppressant is expected. Dose reduction and close follow up of blood levels is recommended	• **Use PAX under close medical supervision only** (transplant expert etc.) • Consider non-interacting alternatives such as remdesivir or molnupiravir
	Everolimus	up				
	Tacrolimus	up		23-46 hours		
	Sirolimus	up		62 hours		
Narcotics	Fentanyl	up	Fatal respiratory depression	Depending on dosage form		**Do not use PAX** unless careful monitoring is possible
	Methadone	down	Withdrawal	8-59 hours		**Do not use PAX** unless careful monitoring is possible
PDE 5 inhibitor	Sildenafil (Revatio)	up	Hypotension, syncope, erection	4 hours	See table below for erectile dysfunction	**Do not use PAX**
	Vardenafil (Levitra, B-On, Vardenafil Inovamed)	up	Hypotension, syncope, erection	4-6 hours	AUC increase 49-fold, Cmax increase 13-fold	**For pulmonary hypertension - Do not use PAX** **For erectile dysfunction – stop Vardenafil 24 hours before PAX, resume use 48 hours after the last dose of PAX**
Sedative hypnotics	Midazolam PO	up	Respiratory Failure	2.5 hours	Specific instructions for patients on SOS midazolam	**Do not use Midazolam PO, if patient on PAX**

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Recommendations for Paxlovid Use in Patients on Interacting Medications

Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
Alpha Blockers	Alfuzosin (Xatral, Alfucal)	up	hypotension	10 hours	Low chance of urinary retention Cmax+AUC x 2	• Stop Alfuzosin • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
	Tamsulosin	up	hypotension	14 hours	Possible to continue treatment and monitor orthostatic hypotension and blood pressure	• Consider stopping Tamsulosin • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
Amphetamines	Attent (D-amphetamine Sacch., Amphetamine Aspartate, D-amphetamine Sulf., Amphetamine Sulf.)	Up (via CYP2D6)	Serotonin syndrome		Possible to continue treatment but monitor BP and signs of serotonin syndrome	• Consider stopping amphetamines • Start PAX • Restart amphetamines 24 hours after last dose of PAX
	Methylphenidate (Ritalin, Concerta)				Not metabolized via CYP	Use PAX, no interaction expected
Analgesics and Narcotics	Dipyrone (Optalgin)				CYP3A4 weak inducer	Use PAX regardless of OPTALGIN
	Pethidine	up	Respiratory depression	2.5-8 hours		• Use PAX minimum 12 hours after pethidine • Do not use Pethidine if patient on PAX
	Buprenorphine	up	Not clinically significant			Use PAX
	Oxycodone	up	Sedation, respiratory depression	4 hours	Monitor sedation and consider reducing doses	Use PAX

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Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
	Hydrocodone	up	Sedation, respiratory depression			• Use PAX • Reduce hydrocodone dose by 50% during PAX • Resume normal dose 24 hours after stopping PAX
	Tramadol	up	Sedation	6-8 hours	Possible reduced efficacy due to reduced active metabolites	Use PAX
	Fentanyl	up	Fatal respiratory depression	Depends on dosage form		**Do not use PAX** unless careful monitoring is possible
	Methadone	down	withdrawal	8-59 hours		**Do not use PAX** unless careful monitoring is possible
Anti-arrhythmic	Amiodarone (Procor, Amiocard)	up	Arrhythmias	50 days	No clinical effect expected	• Stop amiodarone • Start PAX 24 hours later • Restart 24 hours after last dose of PAX
	Dronedarone (Droncor, Multaq)	up		20 hours	No clinical effect expected	• Stop dronedarone • Start PAX 24 hours later • Restart 24 hours after last dose of PAX
	Flecainide (Tambocor)	up		12-27 hours	Arrhythmias as of 2^{nd}-3^{rd} day	**Do not use PAX**
	Propafenone (Profex, Rythmex)	up		5-8 hours	Arrhythmias as of 2^{nd} day	**Do not use PAX**
	Disopyramide (Rythmical)	up		10 hours		**Do not use PAX**
Anticancer	Abemaciclib (Verzenio)	up	Myelosuppression GI toxicity	18 hours		• Stop Abemaciclib • Start PAX 24 hours later • Restart 24 hours after last dose of PAX
	Apalutamide (Erleada)	-	Decreased PAX	3 days		**Do not use PAX**

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Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
	Ado-trastuzumab-emtansin (Kadcyla)	up		4 days	Toxicity of attached chemo	• Use PAX • Resume Kadcyla 24 hours after last dose of PAX
	Ceritinib (Zykadia)	up	QTc prolongation GI toxicity	41 hours	If impossible to stop, reduce dose by 30%	• Stop Ceritinib • Start PAX 48 hours later • Restart 24 hours after last dose of PAX
	Dasatinib (Sprycel)	up	Myelosuppression QTc prolongation	3-5 hours		• Stop Dasatinib • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
	Encorafenib (Braftovi)	up	QTc prolongation	3.5 hours		• Stop Encorafenib • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
	Fostamatinib (Tavalisse)	up	Hepatic adverse effects	15 hours	Monitor adverse reactions	Use PAX
	Ibrutinib (Imbruvica)	up	• Arrhythmias • GI toxicity • Nephrotoxicity • Hemorrhage	4-6 hours	Possible to reduce ibrutinib dose to 140 mg and monitor toxicity	• Stop Ibrutinib • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
	Ivosidenib (לא רשומה בארץ)	up	QTc prolongation Nephrotoxicity	58-129 hours		**Do not use PAX**
	Lorlatinib (Lorbrena)	up	Adverse effects such as bradycardia	24 hours	• Reduce from 100mg-75mg daily • Reduce from 50mg to 25mg daily	• Use PAX • Reduce lorlatinib dose (see comments)
	Neratinib (Nerlynx)	up	GI toxicity	7-17 hours		• Stop Neratinib • Start PAX 24 hours later • Restart 24 hours after last dose of PAX

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Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
	Nilotinib (Tasigna)	up	• QTc prolongation • Myelosuppression • Cardiotoxicity • Hemorrhage	17 hours		• Stop Nilotinib • Start PAX 24 hours later • Restart 24 hours after last dose of PAX
	Venetoclax (Venclexta)	up	Myelosuppression GI toxicity	26 hours	If patient on steady daily dosage, possible to reduce venetoclax dose by 75%	• Stop venetoclax • Start PAX 24 hours later • Restart 24 hours after last dose of PAX
	Vinblastine (Blastovin)	up	• Myelosuppression • GI, pulmonary toxicity • Neurotoxicity	25 hours		• Stop Vinblastine • Start PAX 24 hours later • Restart 24 hours after last dose of PAX
	Vincristine (Vincristine teva)	up	• Neuromuscular, GI toxicity • Myelosuppression	85 hours		**Do not use PAX**
Anticoagulants/ antiplatelets	Warfarin (Coumadin)	changes	-	40 hours	Variable effects	Continue warfarin, monitor INR
	Rivaroxaban (Xarelto)	up	bleeding	5-9 hours	• Consider risk of stopping anticoagulation for specific patient. • Possible to use alternative anticoagulant. • If risky to stop, don't use PAX	• Stop rivaroxaban • Consider replacing with enoxaparin/apixaban • Start PAX 24 hours later. • Restart 24 hours after last dose of PAX
	Apixaban (Eliquis)	up	bleeding	12 hours	• Reduce Apixaban dose to 2.5mg x 2/d. • If that is usual dosage then replace with enoxaparin. • If risky to stop, don't use PAX	• Consider stopping/reducing apixaban (see comments) • Consider replacing with enoxaparin • Start PAX 12 hours later. Restart 24 hours after last dose of PAX

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	Edoxaban	up	bleeding	10-14 hours	• No info on ritonavir interaction although potentially strong P-gp inhibitor, so dose reduction may be required. • Until further info, **do not use with PAX**	• Stop edoxaban • Consider replacing with enoxaparin /apixaban • Start PAX 24 hours later. • Restart 24 hours after last dose of PAX
	Dabigatran (Pradaxa, Dabigatran Teva)	up	bleeding	12-17 hours	Dabigatran levels my rise due to P-gp inhibition.	• Stop dabigatran. Consider Enoxaparin or Apixaban. • Start PAX 24 hours later. • Restart 24 hours after last dose of PAX
	Ticagrelor (Brilinta)	up	bleeding	9 hours	Ticagrelor converted to active drug via CYP3A4	• Consider stopping ticagrelor (if possible). • If impossible, do not use PAX
	Prasugrel	No effect			No clinically relevant effect on platelet activity	Use PAX
	Clopidogrel (Plavix, Clood, Clopidexcel)		Less conversion to active metabolite		Converted to active metabolite mostly by CYP2C19, so little effect is expected on platelet activity	• Use PAX • Consider not using PAX if close proximity (4 weeks) to PCI or acute ischemia (e.g. CVA, ACE)
Antidepressants	Bupropion (Wellbutrin)	down	depression	20 hours		Continue bupropion, monitor depression
	Trazodone (Trazodil)	up	Nausea, hypotension, dizziness	7-10 hours		Continue Trazodone, monitor patient
	Amitriptyline	up	Adverse effects - dry mouth, blurred vision etc.		Monitor adverse effects	• Continue antidepressants • Use PAX
	Imipramine					
	Desipramine					
	Nortriptyline					
	Fluoxetine		Serotonin syndrome			
	Paroxetine					
	Sertraline					

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	Mirtazapine	up	Serotonin Syndrome, prolonged QT	30-50 hours	Monitor serotonin syndrome	• Use PAX • Reduce mirtazapine dose to minimum
	Remotiv	PAX down			Mild reduction of PAX	Use PAX
Anti-diabetic	Repaglinide	up	hypoglycemia	12 hours	Monitor hypoglycemia signs	Use PAX
	Saxagliptin			2.5 hours		• Use PAX • Max dose saxagliptin: 2.5 mg/day
Anti-epileptics	Carbamazepine Phenobarbital Phenytoin Primidone	-	• Decreased PAX • Increased anti-epileptic agents	15 hours 80 hours 22 hours	CYP34 inducers	**Do not use PAX**
	Valproic acid	down	Possible reduced efficacy	9-19 hours		Consider using PAX
	Lamotrigine	down	Possible reduced efficacy	33 hours		Consider using PAX
	Midazolam Diazepam	up	Respiratory depression			Do not use if patient on PAX
	Clobazam	up		36-42 hours	Monitor adverse effects	Use PAX
	Cenobamate		Mild decrease PAX	50 hours		Use PAX
Anti-fungal	Isavuconazole	up	Ritonavir down	130 hours		**Do not use PAX**
	Itraconazole	up	Itraconazole up	34-42 hours	Consider dose reduction if necessary	Use PAX, monitor adverse effects
	Ketoconazole	up	Prolonged QT	8 hours	• AUC X 3.4 • If impossible to stop ketoconazole, do not use PAX	• Stop ketoconazole • Start PAX 24 hours later. • Restart ketoconazole 24 hours after last dose PAX

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	Voriconazole (Vfend, Vori Teva, Vortimal)	down		6-8 hours	• Low dose causes reduced AUC 39%, and reduced CMAX 24%. • Consider risk of lower voriconazole levels	• Continue voriconazole • Use PAX
Anti- gout	Colchicine	up	Colchicine toxicity	27-34 hours	Monitor signs of colchicine toxicity. Usually GI first	• Renal/ Hepatic failure - Do not use PAX • Normal renal/hepatic function – max. colchicine dose is 0.5 mg/day. • Resume normal dose 14 days after stopping PAX
Anti-histamine	Fexofenadine Loratadine	up	Adverse effects		Monitor adverse effects	Use PAX
Anti-infective	Clarithromycin	up	QT prolongation Decreased active metabolite	7-9 hours	Consider switching to roxithromycin or azithromycin	• Use PAX • Max clarithromycin dose: 1 gr/day • eGFR 30-60ml/min reduce dose 50% • eGFR <30ml/min reduce dose 75%
	Erythromycin	up	QT prolongation	2-3 hours	Consider switching to alternative macrolide (roxi/azithromycin)	• Stop erythromycin • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
	Rifabutin	up	Side effects	45 hours	With chronic ritonavir dose of rifabutin reduced to: 150 mg x 3/week	• Stop rifabutin • Start PAX • Restart 24 hours after last dose of PAX
	Bedaquiline (Sirturo)	up		5.5 months	Very long half-life, not affected by 5 days treatment	Use PAX, monitor patient for side effects
	Fusidic acid	up	Hepatotoxicity			**Do not use PAX** unless possible to stop fusidic acid

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	Rifampin		PAX ineffective		Reduced PAX concentrations	**Do not use PAX**
	Atovaquone, Proguanil (Malarone)	down	Atovaquone effectivity reduced		Consider effect of reduced atovaquone efficacy or do not use PAX	Use PAX
	Delamanid		Up metabolite that causes QT prolongation	38 hours		Use PAX if possible to monitor QT
Anti-migraine agents	Eletriptan	up		4 hours		• **Do not use PAX concomitantly**. • Wait at least 72 hours after PAX before resuming treatment with eletriptan
	Ubrogepant	up		5-7 hours		• **Do not use concomitantly with PAX.** • Wait at least 24 hours between PAX and ubrogepant, and vice versa.
	Rimegepant	up		11 hours	AUC may increase 4-fold	• **Do not use PAX concomitantly**. • Wait at least 24 hours between PAX and rimegepant, and vice versa.
Antipsychotics	Haloperidol Risperidone Thioridazone	up	Adverse effects of anti-psychotic		Due to CYP2D6 inhibition	Use PAX, monitor adverse effects of antipsychotic agent
	Clozapine	up	QT prolongation	12 hours	Withdrawal effects if stopped abruptly	**Do not use PAX**
	Quetiapine	up	QT prolongation	6 hours	Withdrawal effects if stopped abruptly	**Do not use PAX**
	Pimozide (Orap)	up	QT prolongation	55 hours		**Do not use PAX**
	Lurasidone	up		18-40 hours		**Do not use PAX**
	Ziprasidone	-				Use PAX

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Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
Calcium Blockers	Amlodipine	up	hypotension	30-50 hours	• Consider risk of stopping amlodipine. • Hypotensive effect continues 72 hours	• Stop amlodipine (or reduce dose by 50%) • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
	Lercanidipine	up	hypotension	10 hours	• Consider risk of stopping lercanidipine • Hypotensive effect continues 24 hours	• Stop lercanidipine • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
	Diltiazem	up	Hypotension, bradycardia	IR: 3-4.5 hours ER: 5 hours	AUC up by 25% only Monitor patient for adverse effects	Continue diltiazem (consider dose reduction)
	Verapamil	up	Hypotension, bradycardia	3-7 hours	Monitor patient for adverse effects	Continue verapamil (consider dose reduction)
	Nifedipine (Nifedilong)	up	hypotension	2-5 hours	ER so starts decreasing after 24 hours (24 hours+ 5 X $t_{1/2}$)	• Stop Nifedipine • Start PAX 24 hours later • Restart 24 hours after last dose of PAX
Cardiac Glycosides	Digoxin	up	bradycardia	36-48 hours	Mostly renal excretion. AUC elevated 22%.	• Continue digoxin if renal function is unchanged • Monitor Patient • Use PAX as usual
Cardiovascular agents	Eplerenone	up	Hyperkalemia	3-6 hours		• Stop eplerenone. Start PAX 24 hours later. • If impossible to stop eplerenone, do not give PAX. • Restart 24hours after last dose of PAX

הצעות לשימוש מושכל ב-PAXLOVID בחולה מטופל בתרופות כרוניות
גרסה 8 (13/7/2022)

Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
Cystic fibrosis transmembrane conductance regulator potentiators	Ivacaftor (Kalydeco)	up		12 hours	Reduce dose: Stop evening dose of ivacaftor. Take morning dose of one ivacaftor tablet on day 1 of PAX, and another morning dose on day 5. Resume standard daily dosing (morning and evening) on day 9.	Reduce dosage when given with PAX - see comments
	Elexacaftor / Tezacaftor / Ivacaftor (Trikafta)	up		27 hours / 25 hours / 15 hours	Reduce dose: Stop evening dose of ivacaftor. Take morning dose of two elexacaftor / tezacaftor / ivacaftor tablets on day 1 of PAX, and another morning dose on day 5. Resume standard daily dosing (morning and evening) on day 9.	Reduce dosage when given with PAX - see comments
	Tezacaftor / Ivacaftor (Symdeko)	up		15 hours / 13.7 hours	Reduce dose: Stop evening dose of ivacaftor. Take morning dose of one tezacaftor / ivacaftor tablet on day 1 of PAX, and another morning dose on day 5. Resume standard daily dosing (morning and evening) on day 9.	Reduce dosage when given with PAX - see comments
Endothelin Receptor antagonists	Bosentan	up		5 hours		Discontinue Bosentan at least 36 hours prior to PAX
	Riociguat (Adempas)	up		12 hours	Consider dose reduction if hypotension occurs	Use PAX, monitor for hypotension
HCV antivirals	Elbesavir/ grazoprevir (Zepatier)	up	ALT elevations	24 / 31 hours		Monitor ALT Use PAX as usual

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גרסה 8 (13/7/2022)

Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
	Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)			0.5/17/36 hours		Continue Vosevi, use PAX as usual
Statins/Lipid modifying	Lovastatin	up	rhabdomyolysis	2 hours	If risk of stopping lovastatin is high, change to rosuvastatin 10 mg/day	• Stop lovastatin • Start PAX 12 hours later • Restart 48 hours after last dose of PAX
	Simvastatin	up		unknown	If risk of stopping simvastatin is high, change to rosuvastatin 10 mg/day	• Stop simvastatin • Start PAX 12 hours later • Restart 48 hours after last dose of PAX
	Atorvastatin	up		14 hours	3A4+others metabolism. Possible to continue and monitor signs of rhabdomyolysis	• Consider temporary stop • Start PAX • Restart 24 hours after last dose of PAX
	Rosuvastatin	up		20 hours	3A4 inhibitor so PAX increases (metabolism minor 3A4)	Decrease dose to 10 mg daily during PAX treatment
	Lomitapide	up	Hepatic enzyme elevation	40 hours	• AUC increase 27-fold • Monitor signs of rhabdomyolysis	• Stop Lomitapide • Start PAX 12 hours later • Restart 48 hours after last dose of PAX
	Pravastatin	No effect		3 hours		Use PAX
Contraceptive and hormonal therapy	Ethinyl estradiol	down	Pregnancy	13-17 hours	PAX induces 3A4 so contraceptive levels drop	• Continue contraceptive plus additional measures • Use PAX as usual
	Elagolix (Orilissa)	up		4-6 hours	Non clinically relevant interaction due to short duration of PAX	Use PAX
Immuno-suppressants	Cyclosporine	Up		19 hours	• Elevated levels of immunosuppressants are expected. • Dose reduction and close	• **Use PAX under close medical supervision only** (transplant expert etc.) • Consider non-interacting
	Tacrolimus	up		23-46 hours		
	Everolimus	up		30 hours		

Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
	Sirolimus	up		62 hours	follow-up of blood levels is recommended	alternatives such as remdesivir or molnupiravir • If immunosuppressant was stopped, resume 24 hours after last PAX
LABA	Salmeterol	up	QT prolongation, tachycardia	5.5 hours	Systemic exposure possible via inhalation	• Consider safety of stopping • Stop salmeterol • Start PAX 12 hours later • Restart 24 hours after last dose of PAX
Sedative hypnotics/ Sleeping aids	Alprazolam	up	sedation	10 hours		Decrease dose to 50% Use PAX
	Clonazepam	up	sedation	30 hours	• Monitor for withdrawal effects. • Possible to replace with lorazepam or oxazepam in usual doses as needed	• Stop Clonazepam • Start PAX 12 hours later • Restart 48 hours after last dose of PAX
	Zolpidem	-	-	3 hours	Clinically insignificant interaction	Use PAX
	Zopiclone	up	sedation	5 hours		• Use PAX • Max dose zopiclone 5mg
	Brotizolam	up	sedation	3 hours		• Use PAX • Reduce brotizolam dose to 50%
	Midazolam IV	up	Resp. failure			Use with caution if patient on PAX
	Diazepam (Assival)	up	extreme sedation and respiratory depression	~50 hours	• Monitor for withdrawal effects. • Possible to replace with lorazepam or oxazepam in usual doses as needed	• Stop Diazepam • Start PAX 12 hours later • Restart 48 hours after last dose of PAX
	Clorazepate (Tranxal)	up	extreme sedation and respiratory depression	~2.5 hours		• Stop Clorazepate • Start PAX 12 hours later • Restart 48 hours after last dose of PAX

Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
	Oxazepam	-		6-20 hours		Use PAX
	Lorazepam	-		10-20 hours		Use PAX
Systemic corticosteroids		up	Side effects			Use PAX as usual
PDEF5 Inhibitors	Sildenafil (Revatio)	up	Hypotension, ischemia			**Do not use PAX (see top table)**
	Sildenafil (Viagra)	up	Hypotension, syncope, erection	4 hours	Reduce dose to 25 mg max in 48 hours	• Stop sildenafil (or reduce dose - see comments) • Return to original dose 24 hours after last dose of PAX
	Vardenafil (Levitra, B-On, Vardenafil Inovamed)	up	Hypotension, syncope, erection	4-6 hours	AUC increase 49-fold, Cmax increase 13-fold	• **For pulmonary hypertension - Do not use PAX** • **For erectile dysfunction – stop Vardenafil 24 hours before PAX, resume use 24 hours after the last dose of PAX**
	Tadalafil	up	Hypotension, syncope, erection	15-35 hours	AUC increase 124% Cmax: no change	• **Use PAX** • **Max. dose 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions.**
Thyroid hormone replacement therapy	Levothyroxine (Euthyrox, Eltroxin, Synthroid)	down	Hypothyroidism	6-8 days	For short term treatment no clinically significant effect is anticipated	Use PAX as usual
Overactive bladder	Fesoterodine	up	Anticholinergic effects	7 hours	• Reduce fesoterodine dose to 4mg/d • If EGFR < 50 ml/min stop fesoterodine while using PAX	• Use PAX • Start PAX 24 hours after last dose of fesoterodine • Reduce fesoterodine dose (see comments) • Return to original dose 24 hours after last dose of PAX

Drug Class	Drug	Effect on conc.	Clinical effect	$T_{1/2}$	Comments	Recommendation
	Mirabegron	up		50 hours	• If EGFR 30-90 ml/min reduce mirabegron to 25 mg/d • If EGFR < 30 ml/min stop mirabegron while using PAX	• Use PAX • Start PAX 24 hours after last dose of mirabegron • Reduce mirabegron dose (see comments) • Return to original dose 24 hours after last dose of PAX
	Solifenacin	up	Anticholinergic effects, QT prolongation	45-60 hours	• If EGFR > 30 ml/min reduce solifenacin dose to 5mg/d • If EGFR < 30 ml/min stop solifenacin while using PAX	• Use PAX • Start PAX 24 hours after last dose of solifenacin • Reduce solifenacin dose (see comments) • Return to original dose 24 hours after last dose of PAX
	Tolterodine	up	Anticholinergic effects	9 hours	• Max tolterodine dose: 2mg/day • If EGFR < 30ml/min stop tolterodine while using PAX	• Use PAX • Start PAX 24 hours after last dose of tolterodine • Reduce tolterodine dose (see comments) • Return to original dose 24 hours after last dose of PAX
	Trospium	no			No effect expected	Use PAX