BC COVID THERAPEUTICS COMMITTEE (CTC)

Practice Tool #3 – Drug-Drug Interactions and Contraindications

July Update:

- NEW guidance on managing the interaction between apixaban and nirmatrelvir/ritonavir.
- Most resources now support drug modifications for the duration of nirmatrelvir/ritonavir treatment and 2 additional days after the treatment finishes (as opposed to 3).

OVERVIEW

General Information

Both components of nirmatrelvir/ritonavir (Paxlovid) inhibit CYP 3A4 an p-gp and have numerous drug-drug interactions, some which contraindicate its use. Ritonavir also inhibits CYP 2D6 to a lesser extent. Nirmatrelvir and ritonavir are themselves metabolized by CYP 3A4, and drugs which induce these enzymes will lead to suboptimal concentrations of nirmatrelvir and ritonavir. Impact of nirmatrelvir/ritonavir on DDIs due to CYP 3A4 inhibition lasts ~2 days after stopping.

The following table was developed to identify drug-drug interactions and contraindications, as well as their potential management strategies. Some management strategies (e.g., DOACs, HIV and cancer medications) were developed in consultation with local experts and the Ministry of Health. This is only a guide. Those prescribing or dispensing nirmatrelvir/ritonavir need to be aware that as this is a new drug and new information is emerging rapidly.

The most comprehensive drug-drug interaction checker with nirmatrelvir/ritonavir was developed by the University of Liverpool and is found here: https://www.covid19-druginteractions.org/checker. ***This tool should be consulted when considering modifying therapy due to drug-drug interactions. Use multiple resources*** *(e.g., LexiComp)* ***as some information may be conflicting or incomplete.*** *When assessing interactions using this website, read the notes section as the advice may be extensive. Some interactions are not listed in the monograph. This tool does not replace clinical judgement and pharmacy/expert consultation.*

An accompanying Practice Tool 6: Drug-Drug Interaction Pre-printed Prescription *can be used to prescribe therapy modifications on the basis of this guidance*

CONTRAINDICATIONS and CAUTIONS (Medical Conditions)

The following medical conditions are either CONTRAINDICATED with nirmatrelvir/ritonavir or CAUTION is required (management strategies may be possible whenever specified; consult an expert if in doubt)

Hypersensitivity to nirmatrelvir or ritonavir	Contraindicated in patients with a history of significant hypersensitivity reactions (e.g., anaphylaxis, toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome)
End-stage liver disease (Child-Pugh C or cirrhosis);	Transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Metabolism of nirmatrelvir/ritonavir may be impacted. Use caution.
Renal Insufficiency (eGFR <30ml/min)	Systemic exposure of nirmatrelvir increases in renally impaired. No

	safety data or dose adjustment guidance is currently available in this population. Monograph list eGFR <30 ml/min as a contraindication; guidance for such patients is forthcoming.
Untreated and treated HIV infection may benefit from consultation with a clinician involved in treatment of HIV (e.g., ID, GP treating HIV or HIV pharmacist)	Treatment should not be delayed or withheld based on viral load, CD4 count or treatment status; however, clinicians who treat HIV can be helpful in patient assessment and management. See also http://bccfe.ca/therapeutic-guidelines/bc-cfe-guidelines-use-paxlovid-and-arvs
Persons with opioid use disorder require counselling and/or expert consultation	Nirmatrelvir/ritonavir increase the levels of fentanyl and risk of fatal overdose. Mitigation strategies should be explored and implemented.

DRUG-DRUG INTERACTIONS and MANAGEMENT

The following drugs interact with nirmatrelvir/ritonavir. Some and are CONTRAINDICATED (management strategies may be possible. Consult https://www.covid19-druginteractions.org/checker before attempting. Drugs that are listed to interact in the monograph but have limited clinical impact are also included.

Legend:
CI-X: Contraindicated due to serious toxicity or loss of virologic response. Stopping the drug does not mitigate interaction due to prolonged half-life, duration of enzyme induction or is not clinically appropriate due to risk or severity of condition
CI-M: Co-administration is contraindicated but management strategies possible (e.g., holding drug or switch)
DDI-M: Significant interaction but management strategies possible by prescriber or with expert consultation, or monitor
OK: Interaction listed in the monograph, but the interaction has low clinical relevance
TI: Therapeutic Index; **T1/2:** Half-life; **AUC:** Area Under Curve (cumulative drug exposure); **↑:** Increase; **↓:** Decrease

Holding, switching and reducing the dose of interacting medications should occur for the duration of nirmatrelvir/ritonavir treatment and 2 additional days after treatment finishes (for a total of 7 days).

Drug	Drug Interaction Type, Information and Management Strategy	
Abemaciclib	DDI-M	Oral anticancer agent. ↑'ed abemaciclib levels. Dose ↓ to 100mg BID w/ BCCA consultation
Alfuzosin	CI-M	↑↑ hypotension. If appropriate, hold drug; restart 2 days after finishing treatment
Almotriptan	DDI-M	↑↑'ed levels. For migraines, use 6.25mg max dose, up to 12.5mg/24h period
Alprazolam	DDI-M	↑↑'ed AUC by 2-5X. If appropriate, hold drug or significantly ↓ dose
ANTIDIABETICS	DDI-M	No drug level changes but hypoglycemia has been observed. Pt should self-monitor Sx and BG
Amiodarone	CI-M	↑↑'ed amiodarone levels. Prolonged T1/2 and narrow TI; could consider hold w/ consultation
Amitriptyline	OK	Small ↑ in amitriptyline levels. Likely sub-clinical. Caution those sensitive to ADRs
Amlodipine	DDI-M	↑'ed AUC by 2X. If BP <130, ↓ dose by 50% during treatment and restart 3 days after finishing
Apalutamide	CI-X	Oral cancer agent. ↑'ed levels leading to seizures. Also an enzyme inducer
Apixaban	DDI-M	↑'ed levels of apixaban; ↑ bleeding. Can ↓ to 2.5mg BID or switch to dabigatran. *See notes
Aripiprazole	DDI-M	↑'ed AUC by 2X. For oral, ↓ dose by 50%; Injectable does not interact
Artesunate	DDI-M	↑'ed AUC by 25%. ↓ dose by 25% w/ infectious diseases consultation
Atazanavir	OK	↑'ed levels but not altering therapy is recommended. Caution those sensitive to ADRs
Atorvastatin	DDI-M	↑'ed levels. Hold atorvastatin during treatment and restart 2 days after finishing

Atovaquone	DDI-M	↓'ed levels by 30-70%. Significance is minimal for prophylaxis. ↑ dose for treatment
Betamethasone	OK	Small ↑ in betamethasone levels. Likely sub-clinical especially with inhaled/topical
Bictagravir	OK	Small ↑ in levels of bictagravir, likely not clinically relevant; caution those sensitive to ADRs
Bosentan	CI-X	Endothelin receptor agonist. ↑bosentan levels. Prolonged T1/2 prohibits holding drug
Bromazepam	OK	Small ↑ in bromazepam levels. Likely sub-clinical. Caution those sensitive to ADRs
Budesonide	OK	Small ↑ in budesonide levels. Likely sub-clinical especially with inhaled/topical
Bupropion	OK	↓'ed bupropion levels; delayed interaction; due to short duration of Rx, likely OK
Buspirone	DDI-M	↑'ed levels; reduce dose to 2.5mg BID during treatment and for 2 days after finishing
Bromocriptine	DDI-M	↑'ed levels; reduce dose by 50% during Rx and for 2 days after finishing and monitor for ADRs
Buprenorphine	OK	↑'ed AUC by ~40%; however, did not change PK in opioid-tolerant patients. Monitor
Cabotegravir	OK	UGT1A1 induction leads to small ↓ in cabotegravir levels but not clinically relevant
Canagliflozin	DDI-M	↓'ed canagliflozin levels due to UGT1A1 induction; delayed DDI; monitor sugars
Cannabis	DDI-M	↑'ed levels of certain metabolite; caution users
Carbamazepine	CI-X	Prolonged enzyme induction; ↓↓ levels of nirmatrelvir/ritonavir
Ceritinib	DDI-M	Oral anticancer drug. ↑'ed levels of ceritinib. Reduce dose by 1/3rd with BCCA consultation
Ciclesonide	OK	↑'ed AUC and Cmax but not clinically relevant as absorbed in the lungs/nasal passages
Cisapride	CI-M	↑↑'ed levels of cisapride leading to cardiac arrythmias. Hold drug if appropriate
Chlordiazepoxide	DDI-M	↑'ed chlordiazepoxide levels; no guidance exists; use caution
Clarithromycin	DDI-M	Small ↑'ed levels; not clinically significant if eGFR≥60ml/min. ↓ by 50% if <60ml/min
Clomipramine	DDI-M	↑'ed levels of active metabolite; may prolong QTc; do not use of dose > 150mg/d
Clonazepam	DDI-M	↑'ed levels of clonazepam; data lacking; ↓ dose by 25-50% if appropriate and/or monitor
Clopidogrel	CI-M	no antiplatelet activity in>40% pts; do not coadminister if high risk of clots; √ if OK w/ specialist
Clorazepate	DDI-M	↑'ed levels of clorazepate; data lacking; ↓ dose by 25-50% if appropriate and/or monitor
Clozapine	CI-X	↑'ed AUC of clozapine and ADRs; difficult to adjust as narrow TI
Cobicistat	DDI-M	Bi-directional DDI; ↑'ed levels of both drugs, but not altering therapy is recommended
Colchicine	CI-M	↑'ed colchicine levels; hold in renal impairment; use 0.6mg/day max if normal eGFR
Cyclosporine	CI-M	↑'ed cyclosporine levels by 25%; narrow TI & requires TDM; consult transplant team
Codeine	OK	Small ↓ in conversion to morphine from codeine and ↓ analgesic effect
Darunavir	OK	↑'ed levels but not altering therapy is recommended. Caution those sensitive to ADRs
Dasatinib	DDI-M	Oral anticancer drug; complex dose adjustments - consult Lexicomp; consult BCCA
Desimipramine	DDI-M	↑'ed AUC of desimipramine; caution those sensitive to ADRs
Dexamethasone	OK	If used in low doses (e.g., for nausea), likely not clinically significant if ≤ 12mg/d
Diazepam	DDI-M	Conflicting data; likely ↑'ed sedation; caution patients; ↓ dose in elderly
Digoxin	CI-M	↑'ed digoxin levels; narrow TI; 50% dose ↓ or hold; TDM may be required; consult pharmacy
Dihydroergotamine	CI-M	Egot toxicity like vasospasm and tissue ischemia; hold PRN drug

Diltiazem	DDI-M	↑'ed diltiazem levels; dose ↓ by 25-50% is recommended if BP <130 or HR <60; monitor
Disopyramidine	CI-X	↑'ed disopyramidine levels; ↑'ed arrhythmia; narrow TI; prolonged effect
Divalproex	OK	↓'ed divalproex levels but delayed DDI and due to short duration likely insignificant
Domperidone	CI-M	↑'ed arrhythmia; hold if clinically appropriate; restart 2 days after finishing
Doxorubicin	CI-M	Liposomal doxorubicin OK; if conventional consult BCCA if doses due during Rx
Doxazosin	DDI-M	Small ↑ in AUC of doxazosin; caution those sensitive to ADRs
Dronedarone	CI-X	↑↑'ed [dronedarone]. Prolonged T1/2 and narrow TI; could consider hold w/ consultation
Dutasteride	OK	↑'ed AUC of dutasteride by 30-40%; clinical significance likely small
Edoxaban	DDI-M	↑'ed levels of edoxaban; one source states ↓ to 30mg; another says just monitor
Efavirenz	OK	Small ↑ in efavirenz levels; likely insignificant due to short duration of Rx; caution re: ADRs
Elagolix	DDI-M	↑'ed elagolix AUC; ↑ suicidality and hepatitis; use 150mg/day max while on Rx
Elbasvir	CI-X	↑'ed risk of transaminitis; also ↑'ed levels of grazoprevir; Consult ID or GI
Eletriptan	CI-M	↑'ed levels of eletriptan by 3-6X; hold PRN drug
Encorafenib	CI-M	Oral cancer agent; ↑'ed encorafenib levels; ↑ QTc; consult BCCA if holding is OK
Enzalutamide	CI-X	Oral anti-androgen for prostate cancer; bidirectional DDI
Eplerenone	CI-M	↑↑'ed K levels; Could consider hold w/ consultation if clinically appropriate
Ergotamine	CI-M	Egot toxicity like vasospasm and tissue ischemia; do not coadminister; hold PRN drug
Eslicarbazepine	CI-X	Like carbamazepine; Prolonged enzyme induction; ↓↓ levels of nirmatrelvir/r
Estazolam	DDI-M	↑'ed levels of estazolam; data lacking; caution if sensitive to sedation
Ethinyl Estradiol	DDI-M	↓'ed contraceptive levels; use back-up contraception while on Rx and for rest of cycle
Everolimus	CI-M	↑'ed AUCs by 15X and Cmax by 4X; consult transplant team if holding OK; TDM difficult
Felodipine	CI-M	↑'ed AUC by several-fold; If BP<130 ↓ dose by 75%; resume normal dose 2 days after Rx
Fentanyl	CI-M	↑↑'ed levels of fentanyl; ↑'ed risk of resp depression; avoid use; counsel opioid users
Fuscidic Acid	CI-M	Systemic only; ↑'ed risk of hepatitis; do not coadminister
Flecanide	CI-X	Fatal arrythmias possible; stopping drug may be difficult; consult expert if holding is OK
Fluoxetine	OK	Small ↑ in fluoxetine levels; caution those sensitive to ADRs
Fluticasone inh.	DDI-M	Conflicting resources; Some state ↑'ed HPA suppression after 7 d; hold if appropriate
Flurazepam	DDI-M	↑'ed levels of flurazepam; data lacking; ↓ dose by 25-50% if appropriate and/or monitor
Fluvoxamine	OK	Small ↑ in fluvoxamine levels; caution those sensitive to ADRs
Fostamatinib	DDI-M	ITP drug; ↑'ed AUC y 2X; decrease dose by 50% in consultation with hematologist
Haloperidol	DDI-M	Complex interaction; consult reference; monitoring for ADRs is recommended
Hydrocodone	DDI-M	Mixed interaction; some metabolites ↑, some↓; monitor for sedation
Hydroxychloroquine	DDI-M	↑'ed levels of hydroxychloroquine may ↑ risk of QTc prolongation; hold if at risk of TdP
Ibrutinib	CI-M	Oral anticancer drug; ↑'ed risk for tumor lysis syndrome; consult BCCA if holding OK
Imipramine	OK	Small ↑ in imipramine levels; caution those sensitive to ADRs

Itraconazole	DDI-M	↑'ed levels of itraconazole by 40%. Use 200mg/day max while on Rx
Ivabradine	CI-M	↑'ed levels of ivabradine and bradycardia. Consult expert if holding is OK
Ketoconazole	DDI-M	↑'ed levels of ketoconazole. Use 200mg/day max while on Rx
Letermovir	CI-M	CMV drug; ↑'ed levels 2-fold; consult ID or transplant if management is possible
Larotrectinib	CI-M	Oral anticancer drug
Lidocaine	DDI-M	IM and IV lidocaine levels may not be adequate; titrate to effect
Lomitapide	CI-M	Cholesterol medication; large ↑ in levels; hepatotoxicity possible; hold drug
Lopinavir	OK	↑'ed levels but not altering therapy is recommended. Caution re: ADRs
Lovastatin	CI-M	↑ in levels of lovastatin; rhabdomyolysis possible; hold drug, restart 2 days after Rx
Lurasidone	CI-X	↑'ed levels by multi-fold. Switching likely clinically not feasible
Macitentan	CI-M	PAH drug; ↑'ed levels by >2-fold; consult resp/cardiology if ↓ dose (cutting tablet) is OK
Maraviroc	DDI-M	↑'ed levels of maraviroc. Could dose ↓ to 150mg BID; consult HIV pharmacist at BCCfE
Mexilitine	DDI-M	Small ↑ in mexiletine levels; no dose change but monitor, especially for CNS side effects
Meperidine	DDI-M	↑'ed levels by~50%; decrease dose and monitor for ADRs
Methadone	DDI-M	↓'ed levels of methadone by 20-40%; may be clinically OK; delayed DDI; monitor
Methamphetamine	DDI-M	Small ↑ in serum levels of methamphetamine; caution methamphetamine users
Methylergonovine	CI-M	Egot toxicity like vasospasm and tissue ischemia; do not coadminister; hold PRN drug
Midazolam	CI-M	↑↑'ed risk of extreme sedation. Hold if clinically appropriate; restart 2 days after Rx
Mirtazapine	DDI-M	↑'ed mirtazapine levels by ~50%. Caution with low doses; ↓ dose if > 15mg due to QTc
Modafinil	DDI-M	Inducer. Small ↓ in nirmatrelvir/r levels. Likely not significant unless dose is high
Morphine	DDI-M	Mixed interaction; some metabolites ↑ while some ↓; monitor for toxicity/efficacy
Nadolol	DDI-M	↑'ed Cmax but no effect on AUC; no dose change but monitor ADRs; caution w/ high doses
Neratinib	CI-M	Oral cancer drug. Potential for serious hepatotoxicity. Consult BCCA if holding OK
Nicardipine	DDI-M	↑'ed nicardipine levels; hypotension, flushing, edema; ↓ dose 25-50% if >60mg/d
Nifedipine	CI-M	Large ↑ in nifedipine levels and cardiac clinical effects; hold if appropriate
Nilotinib	CI-M	Oral cancer agent; ↑'ed nilotinib levels and QTc; Hold in consultation w/ BCCA
Nitrazepam	DDI-M	↑'ed levels of nitrazepam; data lacking; ↓ dose if appropriate and/or monitor
Nortriptyline	OK	Small ↑ levels of nortriptyline; clinically insignificant; caution those sensitive to ADRs
Olanzapine	OK	Small delayed ↓ in levels of olanzapine; likely clinically insignificant
Oxcarbazepine	CI-X	Prolonged enzyme induction; ↓ levels of nirmatrelvir/ritonavir; do not coadminister
Oxybutynin	DDI-M	↑'ed levels of oxybutynin by ~50%; if high dose, consider ↓; caution for ADRs
Oxycodone	DDI-M	↑'ed levels of oxycodone and metabolites 1.5-2.5-fold. Consider dose ↓; caution pt of ADRs
Paclitaxel	DDI-M	IV cancer drug; ↑'ed levels of paclitaxel 2-fold; consult BCCA if dose ↓ OK
Paliperidone	OK	Small potential↑ in paliperidone levels; likely not clinically significant
Paroxetine	OK	Small ↑ in paroxetine levels. Likely sub-clinical. Caution those sensitive to ADRs

Perphenazine	OK	Small ↑ in perphenazine levels. Likely sub-clinical. Caution those sensitive to ADRs
Phenobarbital	CI-X	Prolonged enzyme induction; ↓ levels of nirmatrelvir/ritonavir; do not coadminister
Phenytoin	CI-X	Prolonged enzyme induction; ↓ levels of nirmatrelvir/ritonavir; do not coadminister
Pimozide	CI-X	↑'ed levels of pimozide & arrythmias; do not coadminister; holding not appropriate
Primidone	CI-X	Prolonged enzyme induction; ↓ levels of nirmatrelvir/ritonavir; do not coadminister
Prednisolone	OK	Small/no ↑'ed steroid levels but RX is short term and likely not clinically significant
Prednisone	OK	↑'ed in levels of 20-30% of steroid but RX is short term and likely not clinically significant
Propafenone	CI-X	↑'ed levels of propafenone & arrythmias; holding not appropriate
Quetiapine	DDI-M	Large ↑ in quetiapine levels; ↓ dose to 1/6th in consultation with specialist; hold if for sleep
Quinidine	DDI-X	↑'ed levels of quinidine & arrythmias; do not coadminister; holding not appropriate
Quinine	CI-M	Inconsistent data; very large ↓ and ↑ shown; do not coadminister; hold if appropriate
Ranolazine	CI-M	Antianginal for SX only; potential life-threatening reactions; do not coadminister; can hold
Repaglinide	DDI-M	↑'ed hypoglycemic effect; counsel to monitor sugar; may ↓ dose by 50% at meals PRN
Rifabutin	DDI-M	↑'ed rifabutin AUC by 25-40%; dose reduce in consultation with ID or respirology, as needed
Rifampin	CI-X	Potent enzyme inducer, prolonged DDI; ↓'ed levels of nirmatrelvir/r; do not coadminister
Rifapentine	CI-X	Potent enzyme inducer, prolonged DDI; ↓'ed levels of nirmatrelvir/r; do not coadminister
Rilpivirine	OK	↑'ed levels of rilpivirine by ~20-50%; likely not clinically significant; caution re: ADRs
Ritonavir	OK	Patients taking ritonavir-containing HIV regimens should continue their therapy as is
Risperidone	DD-M	↑'ed risperidone levels leading to ADRs; ↓ dose by 50% if appropriate; can consult specialist
Rivaroxaban	CI-M	↑'ed levels of DOAC and ↑ bleeding risk. Can consider switch to dabigatran *See notes
Rosuvastatin	DDI-M	↑'ed levels of rosuvastatin; hold drug during Rx and resume 2 days later
Ruloxitinib	DDI-M	For polycythemia vera; ↑'ed levels 2-fold; consult hematologist to dose reduce by 50%
Salmeterol	CI-M	↑'ed ADRs like palpitations and ↑ QTc; do not stop if resp SX; can consider salbutamol
Saxagliptin	DDI-M	↑'ed hypoglycemic effect; monitor or use 2.5mg/d during Rx and for 2 days after
Sertraline	OK	Small ↑ in sertraline levels. Likely sub-clinical. Caution those sensitive to ADRs
Sildenafil (ED)	CI-M	Large ↑ in levels. Hold while on nirmatrelvir/ritonavir, can restart 2 days after Rx finishes
Sildenafil (PAH)	CI-X	↑'ed risk for severe hypotension, syncope, visual changes; stopping likely not appropriate
Silodosin	DDI-M	For BPH; large ↑ 3-4X in silodosin levels; hold if appropriate or ↓ dose by 75%
Simvastatin	CI-M	↑ in levels of simvastatin; rhabdomyolysis possible; hold drug, restart 2 days after Rx
Sirolimus	CI-M	↑'ed AUCs by 10X and Cmax by 4X; consult transplant team if holding OK; TDM difficult
St. John's Wort	CI-X	Prolonged enzyme induction; ↓'ed levels of nirmatrelvir/r. Long lasting DDI
Sufentanil	DDI-M	↑'ed AUC of sufentanil by ~50% and risk of respiratory depression; use lower PRN doses
Sunitinib	CI-M	Oral cancer drug; ↑'ed levels of sunitinib by 50% and toxicity; consult BCCA if holding OK
Tacrolimus	CI-M	↑'ed AUCs by 10X and Cmax by 4X; consult transplant team if holding OK; TDM difficult
Tadalafil (ED)	CI-M	Large ↑ in levels. Hold while on nirmatrelvir/ritonavir, can restart 2 days after Rx finishes

Tadalafil (PAH)	CI-X	↑'ed risk for severe hypotension, syncope, visual changes; stopping likely not appropriate
Tamsulosin	DDI-M	↑'ed tamsulosin levels by 2-3-fold but no BP changes were observed; caution pt and monitor
Tenofovir	OK	Slight ↑ in levels; likely clinically insignificant due to duration of Rx
Ticagrelor	CI-M	↑'ed bleeding risk; holding not appropriate unless thrombosis risk low; consult cardiology
Tofacitinib	DDI-M	↑'ed tofacitinib levels; ↓ dose by 50% (from 10mg to 5mg or from BID to QD) during Rx
Tolterodine	DDI-M	↑'ed levels by 2-fold and ADRs; use 2mg/day max while on Rx and for 2 d after stopping
Tramadol	DDI-M	Mixed interaction; some metabolites ↑, some ↓; caution pt re: ADRs
Trazadone	DDI-M	↑'ed levels of trazadone by 2-fold; dose reduce by 50% if over 150mg/d; can hold for sleep
Triazolam	CI-M	↑'ed risk for sedation; hold if clinically appropriate and restart 2d after RX; watch withdrawal
Upadacitinib	DDI-M	Oral cancer agent; ↑'ed upadacitinib levels; >15mg/d is not recommended; consult w/ BCCA
Valproate	OK	Potential ↓ in valproate levels, delayed; likely not clinically relevant due to short Rx
Vardenafil (ED)	CI-M	Large ↑ in levels. Hold while on nirmatrelvir/ritonavir, can restart 2 days after Rx
Vardenafil (PAH)	CI-X	↑'ed risk for severe hypotension, syncope, visual changes; stopping likely not appropriate
Venetoclax	CI-X	Oral cancer drug; ↑'ed levels; CI during ramp-up phase; consult BCCA to √ phase & ↓ dose
Venlafaxine	OK	Small ↑ in venlafaxine levels. Likely sub-clinical. Caution those sensitive to ADRs
Verapamil	DDI-M	↑'ed verapamil levels but resources inconsistent; Monitor for dizziness, low BP and low pulse
Vincristine	DDI-M	↑'ed toxicity like GI, neurotoxicity and marrow suppression consult BCCA if coadministering
Vinblastine	DDI-M	↑'ed toxicity like GI, neurotoxicity and marrow suppression consult BCCA if coadministering
Voriconazole	DDI-M	↓'ed voriconazole levels; consult ID/Resp if clinically acceptable or if TDM is required
Warfarin	DDI-M	Mixed DDI; net effect is a ↓ in INR; monitor INR if possible, especially if high for thrombosis
Ziprasidone	DDI-M	↑'ed levels of ziprasidone by 30-40%; use with caution and monitor for ADRs
Zolpidem	DDI-M	↑'ed risk for sedation; decrease dose by 50% or hold if PRN for sleep
Zopiclone	DDI-M	↑'ed risk for sedation; use max dose of 3.75mg/d or hold if PRN for sleep

DOACs: Rivaroxaban and Apixaban: STEP BY STEP INSTRUCTIONS

Rivaroxaban and **Apixaban** are two of the most common drugs that have drug-drug interactions with nirmatrelvir/ritonavir. Both can be switched to dabigatran. Apixaban can also be dose reduced. Please see notes below pertaining to patients with Cancer-associated Thrombosis (CAT).

Apixaban and Rivaroxaban Management

If on apixaban 2.5 mg BID	Continue unmodified. **Can only be considered if no bleeding event in the last 3 months**
If on apixaban 5 mg BID	Decrease dose to 2.5 mg BID. Patient may cut 5mg tablets in half. Resume apixaban 5mg BID 2 days after Paxlovid ends. **Can be considered if no thrombotic event (stroke or VTE) within the past 3 months**
If taking apixaban for a thrombotic event that has occurred within the past 3 months or has experienced a recent bleeding event in the past 3 months, **DO NOT CO-ADMINISTER. Switch to dabigatran.**	

Rivaroxaban	**DO NOT CO-ADMINISTER. Switch to dabigatran.**

Switching to Dabigatran – SPECIAL AUTHORITY REQUIRED

The switch should only be attempted for patients who can follow clear directions, who can fill the dabigatran prescription and who will be amenable to follow-up by a pharmacist by phone. *Provide clear counselling AND have the patient repeat the directions back. Ensure patient understands that they will NOT take dabigatran with their current DOAC at the same time. Describe/show them the tablets they are to hold.*

Apixaban 5mg is a peach oblong tablet. Apixaban 2.5mg is a round yellow tablet.	Rivaroxaban tablets are peach (10mg), orange (15mg) and brown (20mg)
 Eliquis® (apixaban) Recall Lot HN0063 ...	 *Rivaroxaban 10mg* *Rivaroxaban 15mg*  *Rivaroxaban 20mg*

TO PRESCRIBE:

1. Give the patient a new prescription for dabigatran, dosed according to their eGFR/age/current DOAC dose for 7 days (patients can be switched for up to 10 days and Special Authority approval last for 10 days, but recent data show that 7 days is sufficient. Patients take dabigatran during the 5-day Paxlovid treatment and for 2 days after Paxlovid ends as the enzyme inhibition reverses.)
2. State to hold rivaroxaban or apixaban for the 7 days while taking the dabigatran prescription.
3. Specify on the Paxlovid prescription that this change is being implemented. The pharmacist dispensing Paxlovid will phone the patient to follow-up to ensure the directions are being followed and to remind them to switch back.
4. Fill out Special Authority using eForm. Select “Other” as the reason and choose Paxlovid DDI. If you are not set up for eForm, call Pharmacare directly and apply for SA over the phone. Do not fax the form as it will not be processed in a timely manner. See Appendix on how to do this.
5. If you have doubts that the patient will not follow these directions, do not prescribe Paxlovid.

Dosing of Dabigatran is based on dose of Apixaban, Rivaroxaban, Age and/or eGFR

If the patient is already on dose reduced apixaban (2.5 mg BID) or rivaroxabam 10 or 15mg once daily), switch to dabigatran 110 mg BID.

Do not co-administer dabigatran and Paxlovid with other anticoagulants (e.g., warfarin) or NSAIDs. Low-dose ASA can be continued.

Dabigatran dosing for those on regularly dosed apixaban and rivaroxaban:

If eGFR or renal function available:	
eGFR ≥50	dabigatran 150 mg BID.
eGFR 30-49	dabigatran 110 mg BID.
eGFR <30	do not use dabigatran.

If eGFR or renal function unknown:	
age < 75	dabigatran 150 mg BID.
age ≥75	dabigatran 110 mg BID.

Note on patients with Cancer-associated Thrombosis who are receiving rivaroxaban or apixaban:

- Lowering the dose of apixaban from 5mg BID to 2.5mg BID is an option providing the patient has not had CAT in the past 3 months.
- Dabigatran remains an option as above, but evidence for its use in CAT is limited. Most guidelines do not recommend using dabigatran for treatment of CAT. It seems reasonable to substitute for a short period of time, but once treatment with nirmatrelvir/ritonavir is complete, the patient *must* return to apixaban or rivaroxaban
- A switch to edoxaban is also an option; however, edoxaban is not covered by PharmaCare. Its cost is approximately $3/day. The usual dose of edoxaban is 60mg PO daily; it should be reduced to 30mg PO daily in those with eGFR between 30-50ml/min, those weighing less than 60kg, those taking potent p-gp inhibitors, or in those with high risk of bleeding as there is a very modest interaction between edoxaban and nirmatrelvir/ritonavir as with dabigatran.
- LMWH (approx. $30/day) may also be an option if patients have used injections before and are comfortable with switching. Injection teaching is challenging when patients must self-isolate; this option is for experienced patients only.
- Holding anticoagulation while on nirmatrelvir/ritonavir is possible if the risk/benefit ration is favourable. This can be considered if the patient is beyond 6 months since thrombotic event.
- As with all patients who cannot manage drug-drug interaction from nirmatrelvir/ritonavir, consider remdesivir if patients are at higher risk for breakthrough CAT.

This tool will be updated regularly

Appendix: PharmaCare Special Authority for Dabigatran during Paxlovid Therapy

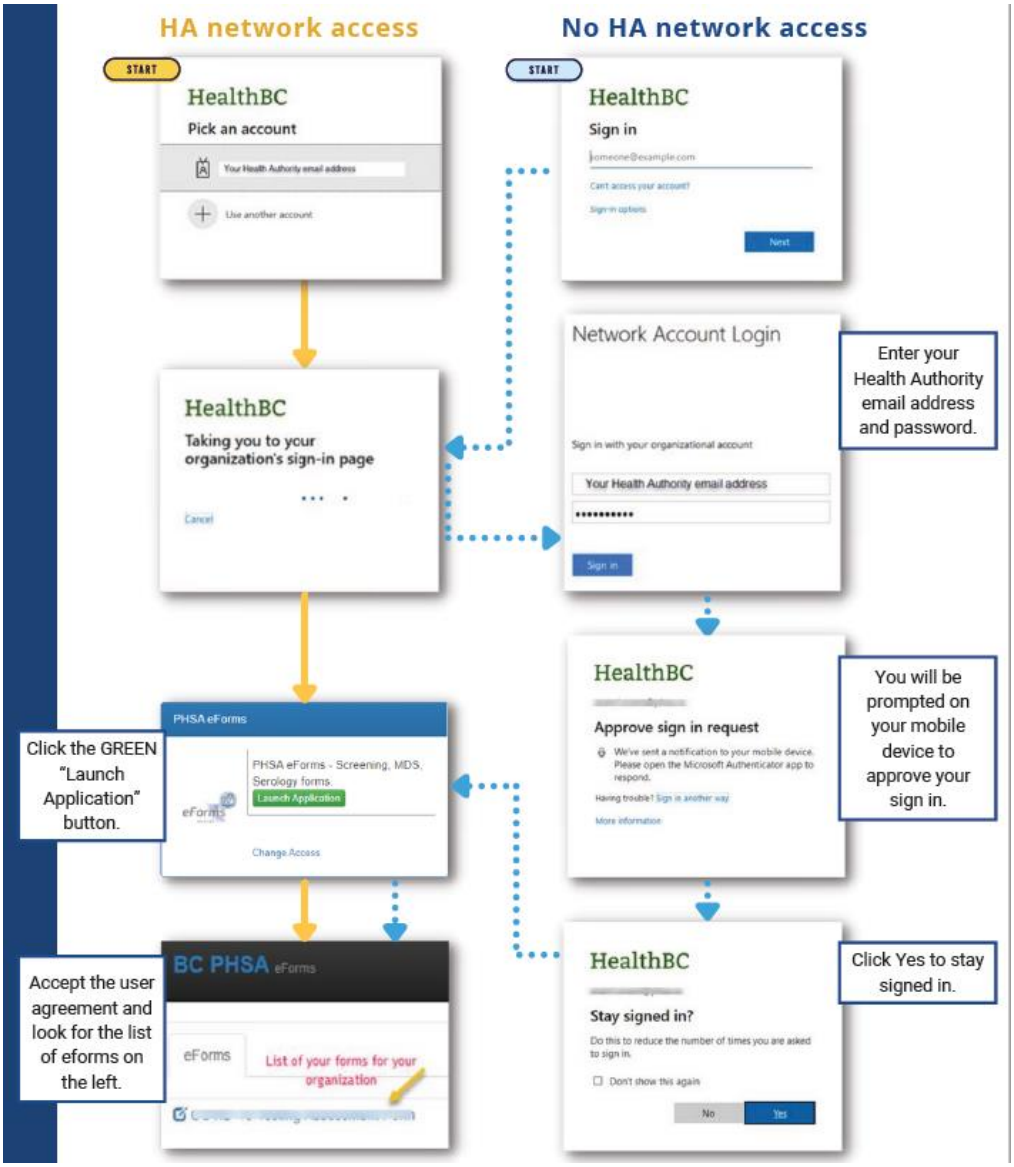
Purpose: This document is intended to describe the steps taken to apply for Special Authority of dabigatran. This document does not describe the drug-drug interaction between DOACs and nirmatrelvir/ritonavir (Paxlovid), nor does it provide any clinical guidance.

Situation: A drug-drug interaction is identified between the patient's DOAC and nirmatrelvir/ritonavir (Paxlovid). Switching the patients DOAC to dabigatran is identified as necessary. Dabigatran is a Limited Benefit drug through PharmaCare and Special Authority is required to obtain coverage.
Please note: Actual reimbursement is dependent upon a patients PharmaCare plan including any deductibles even if Special Authority is approved.

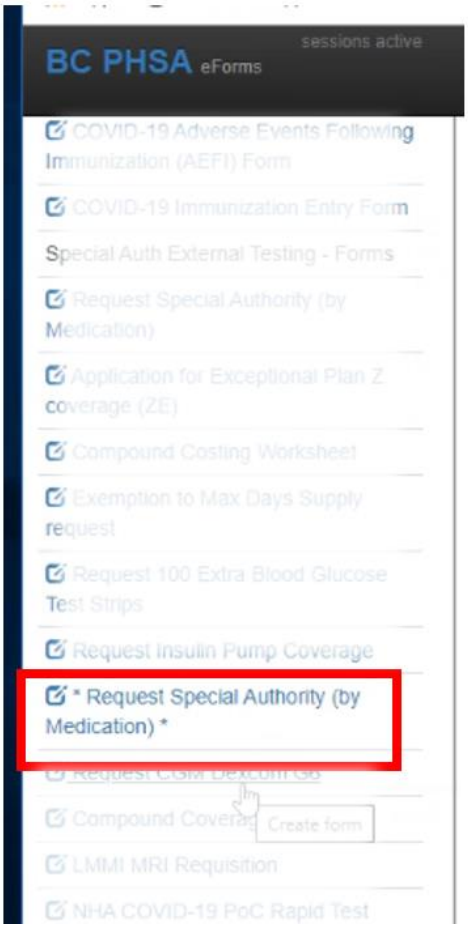
Process:

1. **Please send a prescription for dabigatran to the patient's regular community pharmacy.** This may be different than the pharmacy used to dispense nirmatrelvir/ritonavir (Paxlovid)

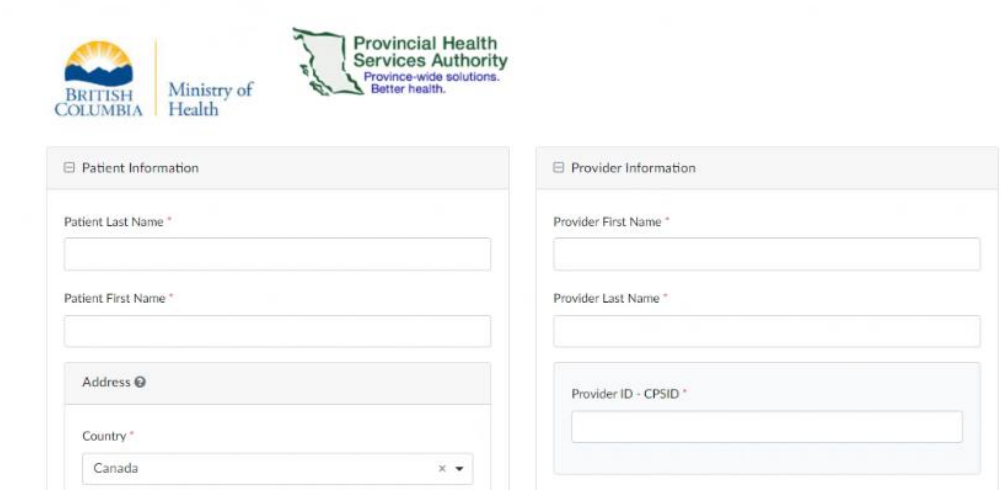
2. Login to eForms through https://www.eforms.phsaehealth.ca on your Health Authority network or through VPN



3. On the left-hand side, **select 'Request Special Authority (by medication)'** from the list of eForms

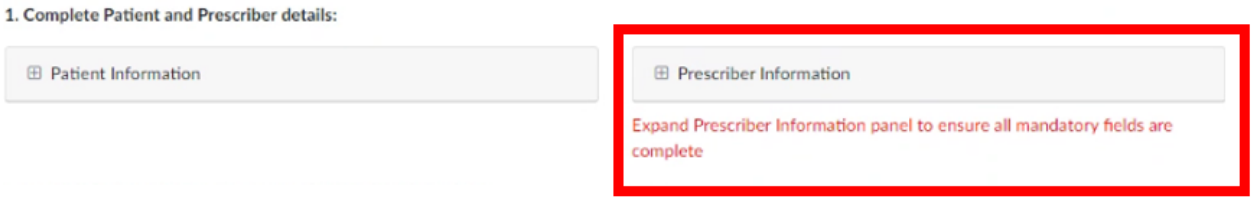


4. Search for the Patient by First Name, Last Name or PHN
5. Search for the Provider by First Name, Last Name or CPSID

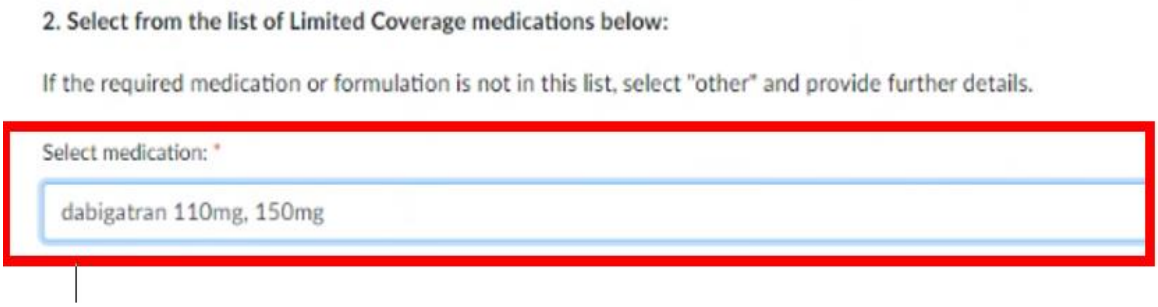


6. Patient information should auto-fill on the left-hand side.

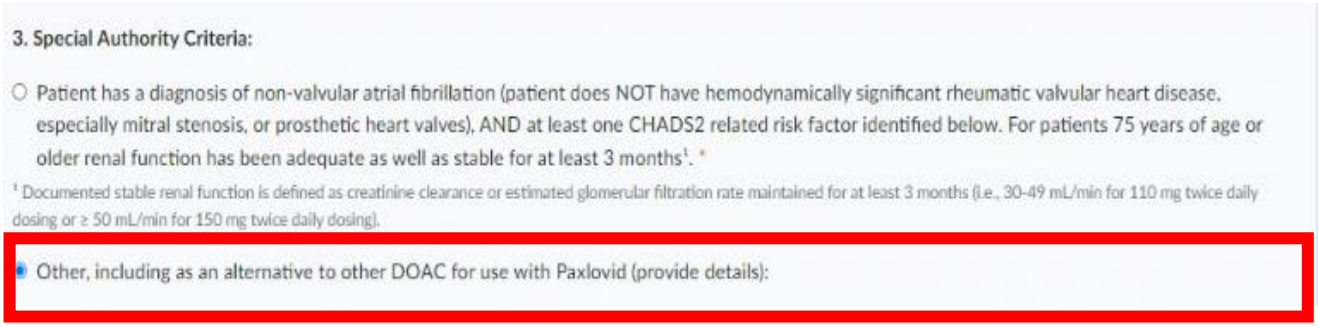
Expand the prescriber information on the right-hand side and enter the fax number.



7. Using the drop down/ search function, **select 'dabigatran 110 mg, 150 mg'**

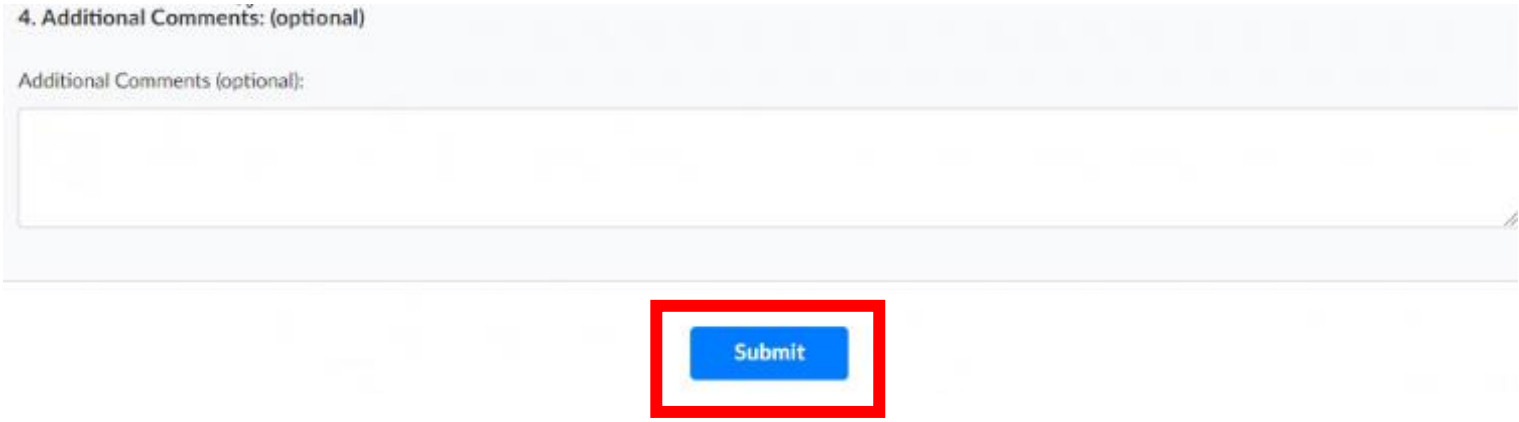


8. Under Special Authority Criteria, **select 'Other, including as an alternative to other DOACs for use with Paxlovid'**



9. Under this section, **select 'Patient is currently on a DOAC that interacts with Paxlovid.** Dabigatran will be co-administered with Paxlovid for up to 10 days. Maximum coverage is 10 days.'

10. Additional Comments are <u>not</u> required.
    Click 'Submit'



11. You will receive a response stating that SA has received your request and the coverage decision will be sent to the fax number entered on the eForm.
    Please note that for this indication, SA approval is done <u>automatically</u> at any time of day or night, however the fax may be delayed.