BC COVID THERAPEUTICS COMMITTEE (CTC)

Practice Tool #3 – Drug-Drug Interactions and Contraindications

September Update:

- NEW guidance on managing patients with unknown renal function or where no recent laboratory work is available
- Appendix with practical information regarding ordering STAT serum creatinine at LifeLabs (see last 2 pages)

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.
Untreated and treated HIV infection may benefit from consultation with a clinician involved in	Treatment should not be delayed or withheld based on viral load, CD4 count or treatment status; however, clinicians who treat HIV can be

treatment of HIV (e.g., ID, GP treating HIV or HIV pharmacist)	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.

Patients with Renal Disease and Serum Creatinine Lab Results

Systemic exposure of nirmatrelvir increases in renal impairment and dose adjustments are used in eGFR 30-60 ml/min. In dose-finding studies, doses of up to 8-fold higher were used in healthy patients with no exposure-related adverse effects noted. While nirmatrelvir and ritonavir are not nephrotoxic and have a wide therapeutic and safety index, no dose adjustment guidance is currently available for patients with eGFR <30 ml/min. The manufacturer is conducting safety and efficacy studies in this population and further guidance is forthcoming; in the meantime, **patients with known eGFR <30 ml/min should not be prescribed nirmatrelvir/ritonavir and be referred for remdesivir if eligible**.

Patients with known renal function of 30-59 ml/min should receive dose-adjusted nirmatrelvir/ritonavir (1 tablet of 150mg nirmatrelvir + 1 tablet of 100mg ritonavir) twice daily for 5 days and such Paxlovid kits are available at pharmacies that carry Paxlovid. Patients with known eGFRs of 60 ml/min or above can receive Paxlovid at a regular unadjusted dose of 300/100 mg nirmatrelvir/ritonavir twice daily for 5 days.

A serum creatinine drawn in the **last 2 years** can be used to guide Paxlovid dosing in patients without end-stage renal disease. Patients without an eGFR result obtained in the last 2 years may be sent for **STAT serum creatinine** at participating LifeLabs (see LifeLabs Appendix). Starting Paxlovid should not be delayed while awaiting SCr results; patients should start Paxlovid at a dose in accordance with their last known renal function and the dose may be modified if the eGFR comes back significantly different than anticipated.

Patients without a serum creatinine drawn in the last 2 years who have no known end-stage renal disease who **are unable to obtain a STAT serum creatinine** may start Paxlovid at a dose in accordance with their last known renal function, or at full dose if no renal disease is anticipated, using clinical judgement. The benefit of preventing severe diseases in such case greatly outweighs the risk of increased exposure to nirmatrelvir/ritonavir. No additional follow-up is required.

Guidance Summary for patients with NO KNOWN end-stage renal disease:

Renal Function on Patient's Profile	Paxlovid Guidance
Serum Creatinine Results Available	
SCr drawn in the last 2 years AND eGFR is ≥ 60 ml/min	Start Paxlovid at regular dose: 2 tablets nirmatrelvir 150mg (=300mg) + 1 tablet ritonavir 100mg PO BID x 5 days
SCr drawn in the last 2 years AND eGFR is 30 to 59 ml/min	Start Paxlovid at a reduced dose: 1 tablet nirmatrelvir 150mg + 1 tablet ritonavir 100mg PO BID x 5 days
SCr drawn in the last 2 years AND eGFR is < 30 ml/min	Do not start Paxlovid. Paxlovid is unlikely to be harmful but sparse dosing data is available. Studies of Paxlovid in end-stage renal disease are ongoing and guidance is forthcoming. Refer for remdesivir is patient meets eligibility criteria.

Serum Creatinine Results Not Available	
No SCr result available on file or SCr drawn more than 2 years ago AND patient cannot draw STAT SCr	Using clinical judgement, start Paxlovid dosed in accordance with the last eGFR available, or at full dose if no previous SCr has ever been drawn.
SCr drawn more than 2 years ago AND patient can draw STAT SCr	Start Paxlovid dosed in accordance with the last eGFR on file. Send patient to nearest laboratory that performs STAT SCr (see Appendix). Dose adjust Paxlovid once SCr is known according to eGFR for the remaining days of therapy.
No SCr result available on file AND patient can draw STAT SCr	Start Paxlovid at regular dose: 2 tablets nirmatrelvir 150mg (=300mg) + 1 tablet ritonavir PO BID. Send patient to nearest laboratory that performs STAT SCr (see Appendix). Dose adjust Paxlovid once SCr is known according to eGFR for the remaining days of therapy.

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; ↓ larotrectinib dose by 50% in consultation with BCCA
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
Ruxolitinib	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

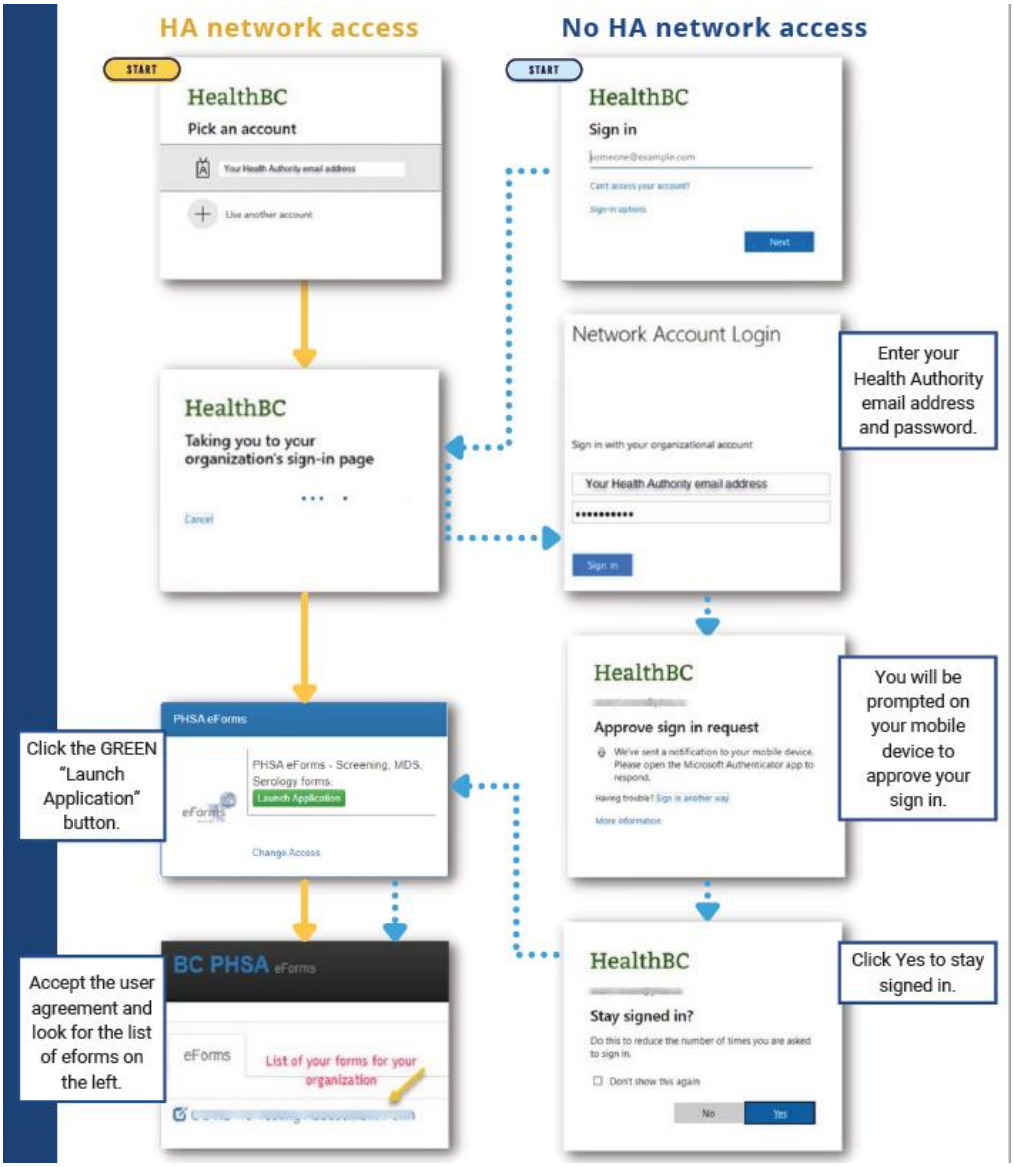
Purpose: This document is intended to describe the steps taken to apply for Special Authority of dabigatran. This document does not describe the drug-drug interaction between DOACs and nirmatrelvir/ritonavir (Paxlovid), nor does it provide any clinical guidance.

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.

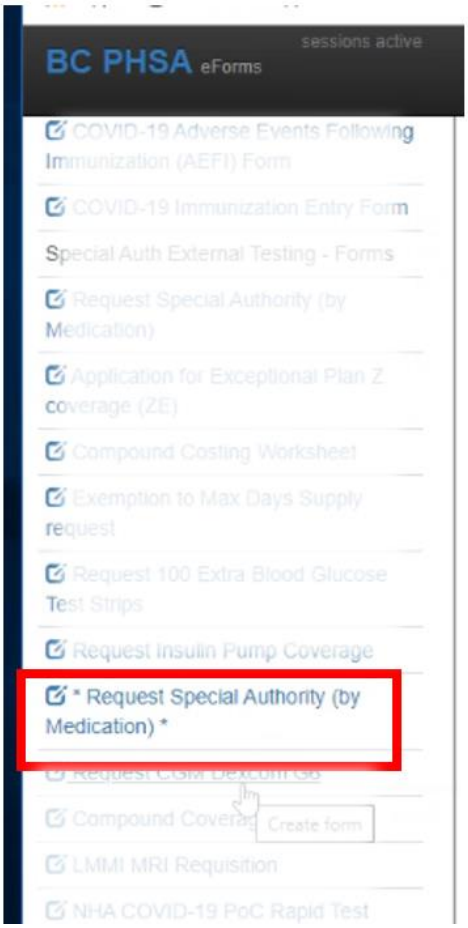
Process:

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)

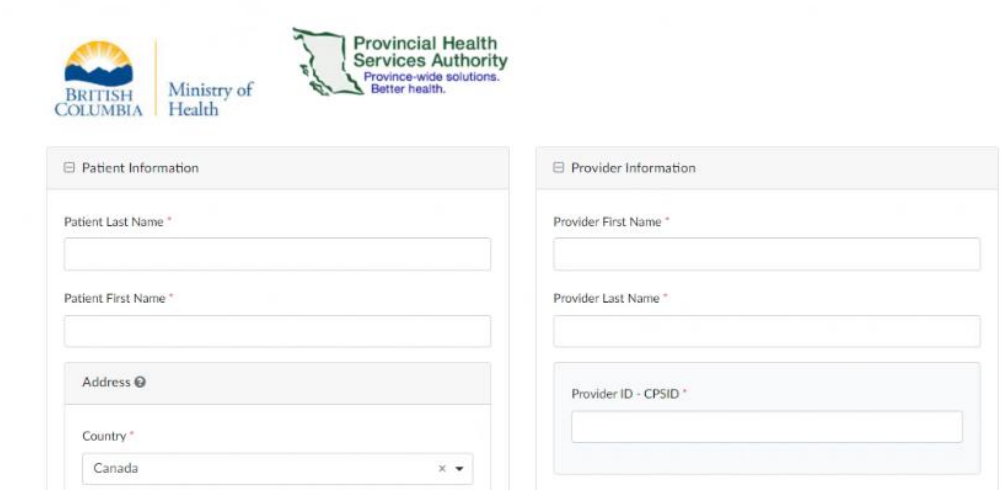
2. Login to eForms through https://www.eforms.phsaehealth.ca on your Health Authority network or through VPN



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

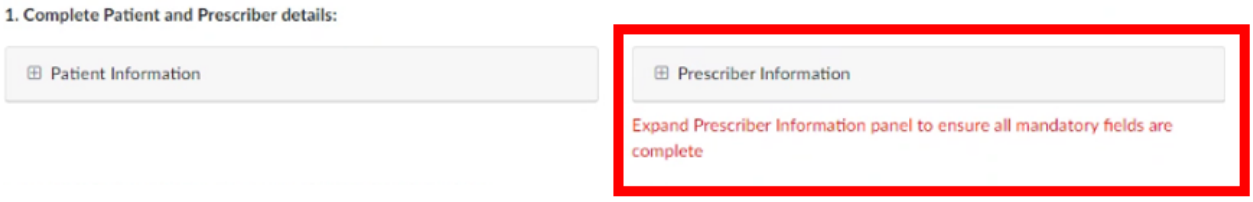


4. Search for the Patient by First Name, Last Name or PHN
5. Search for the Provider by First Name, Last Name or CPSID

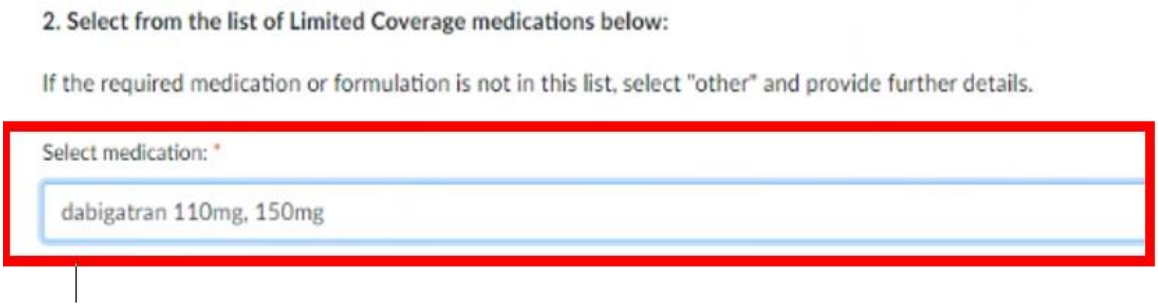


6. Patient information should auto-fill on the left-hand side.

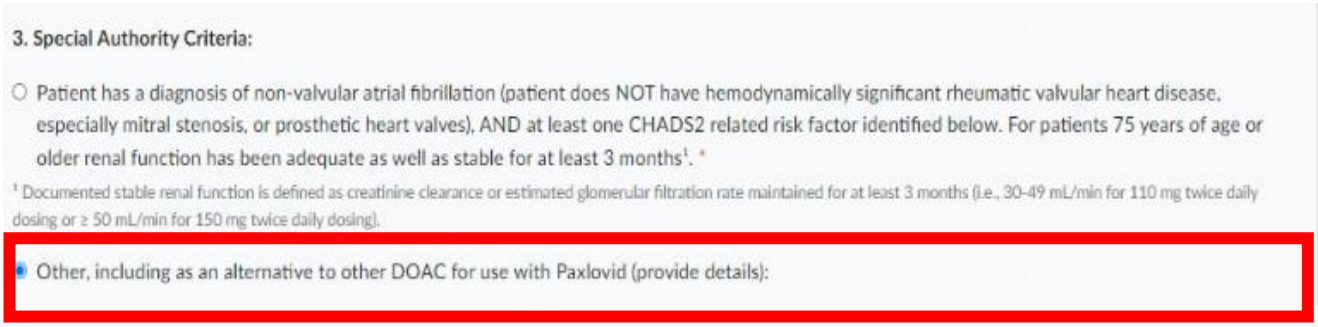
Expand the prescriber information on the right-hand side and enter the fax number.



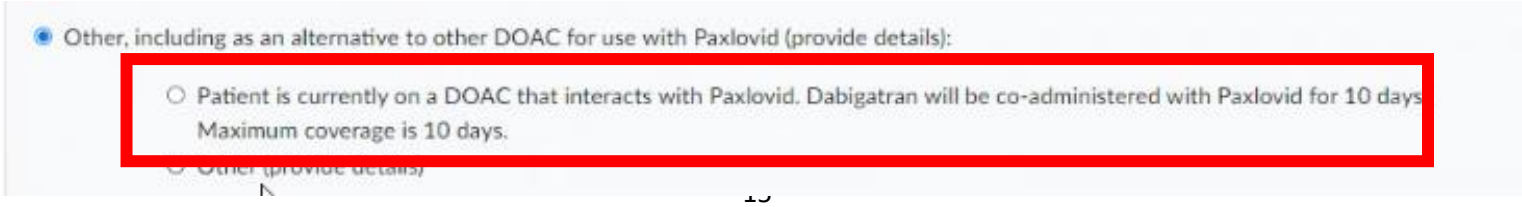
7. Using the drop down/ search function, **select 'dabigatran 110 mg, 150 mg'**



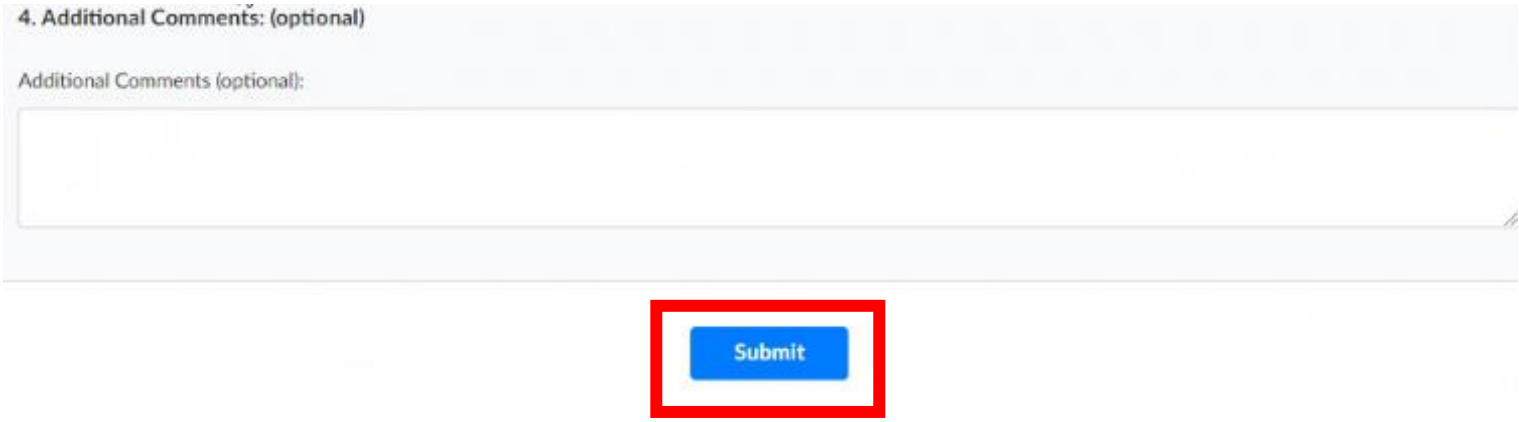
8. Under Special Authority Criteria, **select 'Other, including as an alternative to other DOACs for use with Paxlovid'**



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.

July 18, 2022

BC Health Care Provider Bulletin

INSTRUCTIONS FOR ORDERING LABORATORY TESTING REQUIRED FOR COVID TREATMENT

For patients that require urgent laboratory testing for COVID treatment please follow the steps below to ensure timely access to test results.

For Healthcare Providers

1) Indicate **"STAT/URGENT"** clearly at the top of the requisition
2) Email requisition to **PSCREQSBC@LifeLabs.com** (Please only use this email for STAT/Urgent testing requests)
3) Use patient's first name and last name as the subject line (Note: **do not** include any SIN numbers, health card numbers, or credit card information). The requisition will be able to be retrieved by lab staff after 1hr of being sent
4) Optional: Send copy of the requisition to patient's personal email address so the patient can provide LifeLabs with a copy in the event we cannot retrieve the requisition
5) Direct patient to a non-appointment centre LifeLabs location (please refer to list provided). Alternatively, the patient can visit LifeLabs Location Finder feature at https://locations.lifelabs.com/locationfinder). Please instruct patient to notify staff they are COVID positive and require urgent testing for treatment

For patients

1) Please visit a non-appointment centre LifeLabs location (please refer to list provided). Alternatively, please visit LifeLabs Location Finder feature at https://locations.lifelabs.com/locationfinder
2) Upon checking-in, please notify staff you are COVID-19 positive and that you require urgent lab testing for treatment. LifeLabs staff have procedures for safely collecting from COVID-19 positive patients
3) Notify LifeLabs team member that your requisition was emailed to PSCREQSBC@LifeLabs.com and when it was sent by the healthcare provider

Patients can continue to book appointments at our Appointment Centres if needed. Thank you for your patience and cooperation.

Disclaimer: LifeLabs is accepting requisitions via email to support our patients who present to a Patient Service Centre with an electronic requisition. There is a risk of inappropriate disclosure when emailing a requisition from a public email domain. The patient is responsible for the security of the electronic copy of the requisition when it is on their mobile device or when it is emailed from the patient's public email domain to LifeLabs. LifeLabs will maintain the security of the requisition when it is received by LifeLabs.

LifeLabs Patient Service Centres Serving Walk-in Patients (Non-Appointment Centres)

Please use the LifeLabs Location Finder feature for the most updated list

City	Address	LifeLabs PSC Name
Abbotsford	A8 - 33498 Bevan Ave	Abbotsford
Abbotsford	207-2825 Clearbrook Rd	Clearbrook
Aldergrove	610 - 26310 Fraser Hwy	Aldergrove
Burnaby	104 - 7885 6th St	Burnaby Square
Burnaby	201-4980 Kingsway	Metrotown
Burnaby	103 - 4012 Hastings St	Norburn
Campbell River	Unit #B-5B - 465 Merecroft Rd	Campbell River
Chiiliwack	608 - 8236 Eagle Landing Parkway	Chilliwack
Coquitlam	106 - 1015 Austin Ave	Austin
Coquitlam	208 - 3001 Gordon Ave	Gordon
Courtenay	12 - 1599 Cliffe Ave	Courtenay
Dawson Creek	2 - 705 103 Ave	Dawson Creek
Delta	104-4515 Harvest Dr	Ladner
Delta	122 - 6345 - 120 St	Sunwood
Duncan	208 - 2763 Beverly St	Beverly
Duncan	102 - 149 Ingram St	Ingram
Gabriola	101 - 691 Church St	Gabriola
Gibsons	118 - 1100 Sunshine Coast Hwy	Gibsons
Kamloops	1966 Harrison Way	Harrison Way
Kamloops	202 - 321 Nicola St	Nicola
Kamloops	120 - 546 St. Paul St (Lab)	St. Paul
Kimberley	260 - 4th Ave	Kimberley
Ladysmith	28 - 370 Davis Rd	Ladysmith
Lake Cowichan	1 - 78 Cowichan Lake Rd	Lake Cowichan
Langley	130 - 19653 Willowbrook Dr	Willowbrook
Mill Bay	240 - 2720 Mill Bay Rd	Mill Bay
Mission	103 - 7343 Hurd St	Mission
Nanaimo	155 - 4750 Rutherford Rd	North Town
Nanaimo	106 - 650 S. Terminal Ave	Port Place
Nanaimo	107 - 50 - 10th St	Southgate
New Wetsminister	227 Nelson's Crescent	Sapperton
North Vancouver	305 - 1200 Lynn Valley Rd	Lynn Valley
North Vancouver	201-3650 Mount Seymour Prwy	Park Gate
Parksville	110 - 489 Alberni Hwy	Parksville
Pitt Meadows	102 - 12195 Harris Rd	Pitt Meadows
Port Alberni	106 - 3949 Maple Way	Port Alberni
Port Coquitlam	115 - 1465 Salisbury Ave	Port Coquitlam

City	Address	LifeLabs PSC Name
Prince George	110 - 1699 Victoria St	Prince George
Qualicum	102 - 670 Memorial Ave	Qualicum
Quesnel	15 - 665 Front St	Quesnel
Richmond	170 - 6451 Buswell St	Buswell
Richmond	107 - 6051 Gilbert Rd	Crestwood
Richmond	200 - 5791 No 3 Rd	No 3 Rd
Sechelt	101 - 5531 Inlet Ave	Sechelt
Sidney	101 - 2475 Bevan Ave	Sidney
Sooke	1260 - 6660 Sooke Rd	Sooke
Surrey	19 15300-105th Ave	Guildford
Surrey	112 -15252 - 32nd Ave	Morgan Creek
Surrey	120 - 15331 16th Ave	Peace Arch
Surrey	201-12080 Nordel Way	Scott Rd
Surrey	103 - 9639 137A St	Surrey City Centre 2 (CC2)
Terrace	105 - 4634 Park Ave	Terrace
Tranquille	1 - 685 Tranquille Rd	Tranquille
Vancouver	208 - 1200 Burrard St	Burrard
Vancouver	340 - 3150 East 54th Ave	Champlain Square
Vancouver	206 - 1160 Burrard St	City Centre
Vancouver	2 - 1530 West 7th Ave	Cityview
Vancouver	1506 East Hastings St	East Hastings
Vancouver	701 - 750 Broadway W	Fairmont
Vancouver	2061 42nd Ave West	Kerrisdale
Vancouver	972 West King Edward Ave	King Edward
Vancouver	204 - 180 Keefer St	Main & Keefer
Vancouver	290 - 2184 Broadway W	Regent
Vancouver	6540 Fraser St	Southill
Vancouver	8207 Ontario St	Sunset
Vancouver	407 Gore Ave	Three Pillars
Vancouver	215 - 650 West 41st Ave	Woodridge
Victoria	200 - 1590 Cedar Hill X Rd	Cedar Hill
Victoria	208 - 582 Goldstream Ave	Colwood
Victoria	220 - 1641 Hillside Ave	Hillside
Victoria	102 - 4480 W Saanich Rd	Royal Oak
Victoria	131 - 2945 Jacklin Rd	Westshore
Victoria	230 - 174 Wilson St	Westside
Victoria	200 - 1120 Yates St	Yates
West Vancouver	109 - 575 16th St	Hollyburn