**APPENDIX 5.4: PAXLOVID™ DRUG-DRUG INTERACTIONS**

**How to use this Appendix**

List A summarizes in alphabetical order the medications which are exclusionary for CanTreatCOVID Paxlovid™ arm as well as drugs which may be included with caution. The first column in List A includes drugs that should not be included in CanTreatCOVID because temporary interruption or the monitoring requirements are considered impractical, and the 2nd column in List A includes those drugs that may be included.

List B contains more detail with the rationale.

These lists are based on the [Summary of Product Characteristics (SmPC) of 02 March 2022](https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid/summary-of-product-characteristics-for-paxlovid) (Appendix 5.1). A sub-protocol amendment will be submitted to update List B if and when SmPC is submitted.

Clinical judgement is required to evaluate potential drug interactions. Detailed advice is also available from the Liverpool COVID-19 Drug Interactions Checker website. <https://www.covid19-druginteractions.org/>.

**List A: Alphabetical summary of drugs that may interact with Paxlovid™**

*Note*: You MUST check BOTH columns for each drug

|  |  |
| --- | --- |
| **Drugs NOT to be included in CanTreatCOVID Paxlovid™ arm**  *Drugs that are contraindicated with Paxlovid™ and /or because interruption or monitoring requirements considered impractical in the setting of the clinical trial* | **Drugs which MAY be included in CanTreatCOVID Paxlovid™ arm**  *Drugs which may be used with Paxlovid™ with caution. Those marked with an asterisk have a specific recommendation - see list B for detail. The investigator should consider whether inclusion is appropriate* |
| acalabrutinib  abemaciclib  aliskiren  alfuzosin  amiodarone  amlodipine (≥10 mg daily)  apalutamide  apixaban  astemizole  atovaquone  avanafil  bedaquiline  bepridil  bosentan  carbamazepine  cisapride  clonazepam  clozapine  colchicine  cyclosporine  dasabuvir  delaminid  desipramine  dexamfetamine  diazepam  digoxin  dihydroergotamine  disopyramide  dronedarone  elbasvir  eletriptan  encainide  encorafenib  enzalutamide - discontinued  eplerenone  ergonovine  ergotamine  erythromycin  estazolam  everolimus  fentanyl  flecainide  flurazepam  fusidic acid  glecaprevir  grazoprevir  ibrutinib  imipramine  isavuconazole  itraconazole (systemic)  ivabradine  ketoconazole (systemic)  lercanidipine  letermovir  lomitapide  lovastatin  lurasidone  methylergonovine  methylphenidate  midazolam (oral or parenteral)  neratinib  pethidine  phenobarbital  phenytoin  pibrentasvir  pimozide  piroxicam (systemic)  propafenone  propoxyphene  quetiapine  quinidine  ranolazine  rifabutin  rifampicin  riociguat  rivaroxaban  salmeterol  sildenafil (Revatio®, for pulmonary arterial hypertension or for erectile dysfunction) simvastatin  sirolimus  sodium fusidate  St. John’s Wort (Hypericum perforatum) tadalafil  tacrolimus  terfenadine  ticagrelor | afatinib  alprazolam\*  amitriptyline  amlodipine (2.5 or 5 mg)\*  amprenavir  atazanavir  atorvastatin  budesonide  buprenorphine\*  bupropion  buspirone\*  ceritinib  clarithromycin\*  clopidogrel\*  dabigatran\*  darunavir  dasatinib  dexamethasone  diltiazem  divalproex  efavirenz  ethinylestradiol\*  fexofenadine  fluoxetine  fluticasone propionate  fluvastatin  fosamprenavir  fostamatinib  haloperidol\*  itraconazole (topical)  ketoconazole (topical)  lamotrigine  levothyroxine  loratadine  maraviroc  methadone\*  morphine\*  nifedipine  nilotinib  norbuprenorphine  nortriptyline  paroxetine  pravastatin  prednisolone  raltegravir  risperidone\*  rosuvastatin  sertraline  sulfamethoxazole/trimethoprim  theophylline  thioridazine\*  triamcinolone  trimethoprim  valproic acid  vinblastine  vincristine  voriconazole (topical)  warfarin\*  zidovudine  zolpidem\* |

**Details of Paxlovid™ drug interactions and implications for eligibility for the Paxlovid™ arm of the CanTreatCOVID trial**

Paxlovid™ is subject to a large number of drug interactions. At this stage, the full range of interactions and their clinical significance is incompletely understood, as clinical experience is limited. Trial participants are living in the community and may be advised to isolate due to their COVID-19 infection based on provincial guidelines. This imposes some constraints on drugs which can be safely co-administered with Paxlovid™ as part of this trial.

The following list is based on the summary of product characteristics (SmPC) list of drugs that are contraindicated for use with Paxlovid™ or should be used with caution with Paxlovid™. For each, a recommendation is provided based on a risk assessment. List B will be updated if and when new information becomes available and will be subject to submission for ethics approval prior to implementation. **This list is not exhaustive and if recruiting investigators believe a potential participant is taking a drug which could put the subject at unacceptable risk, the participant should be excluded**. There are some drugs which can be interrupted or adjusted during the trial – a specific recommendation is made for these.

**List B: Details of Paxlovid™ drug interactions and implications for eligibility for drugs that are not recommended or require adjustment with Paxlovid™ in the CanTreatCOVID trial.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Medicinal Product class** | **Drugs in Class with Indicative Effect of Paxlovid™ on Concentration of**  **Medicinal Product** | **Clinical Comments** | **Implications for Eligibility in CanTreatCOVID**  **Paxlovid™ Arm** |
| α1-adrenoreceptor antagonist | ↑alfuzosin | Increased alfuzosin plasma concentrations may lead to severe hypotension.  **Contraindicated.** | **NOT ELIGIBLE** |
| Aldosterone antagonist | ↑Eplerenone | Not recommended with strong 3A4 inhibitor as risk of hyperkalaemia.  **Contraindicated.** | **NOT ELIGIBLE** |
| Amphetamine derivatives | ↑methylphenidate  ↑dexamfetamine | Potential for increased concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended.  **Contraindicated.** | **NOT ELIGIBLE** |
| Analgesics | ↑buprenorphine  ↑norbuprenorphine | The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid  tolerant patients. | **ELIGIBLE** – advise to monitor for opioid toxicity. |
| ↑pethidine  ↑piroxicam (systemic)  ↑propoxyphene | Increased plasma concentrations may result in serious respiratory depression or haematologic abnormalities.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑fentanyl | Ritonavir expected to increase the plasma concentrations of fentanyl. **Contraindicated.** | **NOT ELIGIBLE** |
| ↓methadone | Increased methadone dose may be necessary. Dose adjustment should be considered based on the  patient’s clinical response to methadone therapy. | **ELIGIBLE** – advise to monitor for potential under dosing of  methadone. |
| ↓morphine | Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as a pharmacokinetic enhancer. | **ELIGIBLE** – advise to monitor for morphine underdosing and adjust dose if  required. |
| Antianginal | ↑ranolazine | Potentially increased ranolazine plasma concentrations may result in serious and/or life-threatening reactions.  **Contraindicated.** | **NOT ELIGIBLE** |
| Antiarrhythmics | ↑amiodarone  ↑bepridil  ↑disopyramide  ↑dronedarone  ↑encainide  ↑flecainide  ↑ivabradine  ↑propafenone  ↑quinidine | Potentially increased plasma concentrations may result in arrhythmias or other serious adverse effects.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑digoxin | Potentially increased concentrations. Inhibition of P-gp may decrease renal digoxin clearance. Magnitude of effect not known.  **Contraindicated.** | **NOT ELIGIBLE** |
| Antiasthmatic | ↓theophylline | Ritonavir could potentially decrease theophylline concentrations, but effects unlikely with short course of Paxlovid™. | **ELIGIBLE** – no  theophylline dose adjustment required. |
| Anticancer agents | ↑afatinib  ↑ceritinib  ↑dasatinib  ↑nilotinib  ↑vincristine  ↑vinblastine  ↑fostamatinib | Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of AEs. | **ELIGIBLE** with caution. Advise to monitor symptoms of increased anticancer agent concentrations. |
| ↑acalabrutinib  ↑apalutamide  ↑abemaciclib  ↑encorafenib  ↑ibrutinib | Co-administration not recommended due to potentially increased concentration of anticancer agents and SAEs.  Apalutamide may also decrease exposure of Paxlovid™ and cause potential loss of virologic response.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑neratinib  ↑venetoclax | Increased plasma concentrations which may increase the potential for serious and/or life-threatening reactions.  **Contraindicated.** | **NOT ELIGIBLE** |
| Anticoagulants | Warfarin  ↑↓S-warfarin  ↓↔R-warfarin | Potentially decreased R-warfarin concentrations which may lead to reduced anticoagulation. | **ELIGIBLE** –  recommend check INR on or around day 5 (as self- isolation allows) |
| ↑apixaban | Potentially increased concentrations which may lead to an increased bleeding risk.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑dabigatran | Potentially increased concentrations which may lead to an increased bleeding risk. No effect when co-administered with ritonavir (small effect when given at different time). | **ELIGIBLE –**  recommend taking Paxlovid™ simultaneously with dabigatran |
| ↑rivaroxaban | Potentially increased concentrations which may lead to an increased bleeding risk.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑vorapaxar | Serum concentrations may be increased. Coadministration not recommended.  **Contraindicated.** | **NOT ELIGIBLE** |
| Anticonvulsants | carbamazepine phenobarbital  These drugs are  expected to reduce the concentrations of  Paxlovid™ | Decreased plasma concentrations of Paxlovid™ may lead to loss of virologic response and possible resistance.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↓phenytoin | Ritonavir is expected to decrease the plasma concentrations of phenytoin. Phenytoin may decrease serum levels of ritonavir.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↓divalproex  ↓valproic acid ↓lamotrigine | Ritonavir may decrease the plasma concentrations of anticonvulsants over time but given the short course of Paxlovid™ treatment, no a priori dosage adjustment is  recommended. | **ELIGIBLE** |
| Antidepressants | ↑amitriptyline  ↑fluoxetine  ↑nortriptyline  ↑paroxetine  ↑sertraline | Ritonavir used at higher doses than present in Paxlovid™ may increase concentrations of these antidepressants. With Paxlovid™ no a priori dosage adjustment is recommended. | **ELIGIBLE** |
| ↑desipramine | Dosage reduction is recommended when co-administered. | **NOT ELIGIBLE** |
| ↑imipramine | Nirmatrelvir/ritonavir could potentially increase imipramine concentrations and increase the risk of QT prolongation.  **Contraindicated.** | **NOT ELIGIBLE** |
| Anti-gout | ↑colchicine | Increased colchicine plasma concentrations may result in serious and/or life-threatening reactions.  **Contraindicated.** | **NOT ELIGIBLE** |
| Antihistamines | ↑astemizole  ↑terfenadine | Increased plasma concentrations of astemizole and terfenadine may result in serious arrhythmias from these agents. Note both withdrawn from market globally.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑fexofenadine  ↑loratadine | Ritonavir may increase fexofenadine and loratadine concentrations. | **ELIGIBLE** |
| Antifungals | ↑ketoconazole  ↓voriconazole  ↑itraconazole  ↑isavuconazole | Potentially increased concentrations of ketoconazole, savuconazole and itraconazole, and decreased plasma concentrations of voriconazole.  **Systemic use contraindicated.** | **NOT ELIGIBLE**  when administered systemically.  Topically used agents are not an exclusion criterion. |
| Antimycobacterial | rifampicin | Potentially decreased concentrations of Paxlovid™ may lead to loss of virologic response and possible resistance.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑bedaquiline  ↑delaminid  ↑rifabutin | Potentially increased plasma concentrations of bedaquiline, delaminid and rifabutin.  **Contraindicated.** | **NOT ELIGIBLE** |
| Anti-infective | ↑clarithromycin  ↓14-OH clarithromycin metabolite | Potentially increased plasma concentrations of clarithromycin. Clarithromycin doses greater than 1 gr per day should not be co- administered with Paxlovid™. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%. | **Potentially ELIGIBLE** if no known renal impairment.  **NOT ELIGIBLE**, if known renal impairment. |
| ↑erythromycin | Ritonavir is expected to increase plasma concentrations of erythromycin which may increase risk of QT prolongation.  **Contraindicated.** | **NOT ELIGIBLE** |
| sulfamethoxazole/trim ethoprim | Dose alteration of sulfamethoxazole/trimethoprim  should not be necessary. | **ELIGIBLE** |
| ↑fusidic acid / sodium fusidate | Increased plasma concentrations of fusidic acid and ritonavir.  **Contraindicated.** | **NOT ELIGIBLE** |
| Anti-malarial | ↓atovaquone | Ritonavir is expected to decrease the plasma concentrations of atovaquone.  **Contraindicated.** | **NOT ELIGIBLE** |
| Anti-platelet | ↓clopidogrel | Paxlovid™ may reduce conversion to active drug. Avoid in patients at high risk of thrombosis and those within 6 weeks of stenting. | **NOT**  **ELIGIBLE**, if within 6 weeks of coronary stent or at high risk of thrombosis  Otherwise, potentially eligible. |
| ↑ticagrelor | Expected to substantially increase exposure to ticagrelor.  **Contraindicated.** | **NOT ELIGIBLE** |
| Anti-HIV protease inhibitors | ↑amprenavir  ↑atazanavir  ↑darunavir  ↑fosamprenavir | Potentially increased concentrations of protease inhibitors, but consensus is that no dose adjustment needed. | **ELIGIBLE** |
| Anti-HIV | ↑efavirenz  ↑maraviroc | Potentially increased plasma concentrations of efavirenz and maraviroc. | **ELIGIBLE** – advise monitor for potential side effects. |
| ↓raltegravir  ↓zidovudine | Potentially minor decreased  plasma concentrations of raltegravir and zidovudine. | **ELIGIBLE** – no dose adjustments required. |
| Antiviral | Letermovir  This drug is expected to reduce concentrations of Paxlovid™. | Letermovir is an enzyme inducer so may render Paxlovid™ ineffective.  **Contraindicated.** | **NOT ELIGIBLE** |
| Antipsychotics | ↑clozapine  ↑pimozide  ↑lurasidone  ↑quetiapine | Increased concentrations may result in serious and/or life- threatening reactions.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑Haloperidol  ↑Risperidone  ↑Thioridazine | Ritonavir is likely to increase concentrations of haloperidol, risperidone and thioridazine. | **ELIGIBLE** – with caution and advise to monitor for increased adverse effects. |
| Long-acting beta- adrenoceptor agonist | ↑salmeterol | Ritonavir is expected to increase the plasma concentrations of salmeterol, and may increase risk of QT prolongation, palpitations,  and sinus tachycardia. Therefore, concomitant use is not recommended.  **Contraindicated.** | **NOT ELIGIBLE** |
| Calcium channel antagonist | ↑amlodipine | Ritonavir is expected to increase the plasma concentrations of calcium channel antagonists. | **POTENTIALLY ELIGIBLE,** if taking 2.5 or 5 mg.  **NOT ELIGIBLE**, if taking 10 mg or above |
| ↑diltiazem,  ↑nifedipine | Ritonavir may increase the plasma concentrations of calcium channel antagonists. | **ELIGIBLE** – advise to monitor for side effects. |
| ↑lercanidipine | Expected to substantially increase exposure to lercanidipine.  **Contraindicated.** | **NOT ELIGIBLE** |
| Endothelin receptor antagonists | ↑bosentan  ↑riociguat | Potentially increased concentrations.  **Contraindicated.** | **NOT ELIGIBLE** |
| Ergot Derivatives | ↑dihydroergotamine  ↑ergonovine  ↑ergotamine  ↑methylergonovine | Increased concentrations of ergot derivatives potentially leading to acute ergot toxicity, including vasospasm and ischaemia.  **Contraindicated.** | **NOT ELIGIBLE** |
| GI motility agent | ↑cisapride | Increased plasma concentrations of cisapride, thereby increasing the risk of serious arrhythmias from this agent.  **Contraindicated.** | **NOT ELIGIBLE** |
| Hepatitis C direct acting antivirals | ↑elbasvir/grazoprevir,  ↑glecaprevir/pibrentasvir  ↑dasabuvir | Serum concentrations may be increased by ritonavir, leading to an increased risk of ALT elevations associated with increased glecaprevir and grazoprevir exposure.  **Contraindicated.** | **NOT ELIGIBLE** |
| Herbal products | St. John’s Wort (*Hypericum perforatum*)  This drug is expected to reduce concentrations  of Paxlovid™ | Potentially decreased concentrations of Paxlovid™ may lead to loss of virologic response and possible resistance.  **Contraindicated.** | **NOT ELIGIBLE** |
| HMG-CoA  reductase inhibitors | ↑lovastatin  ↑simvastatin | Increased concentrations resulting in increased risk of myopathy, including rhabdomyolysis.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑atorvastatin  ↑fluvastatin  ↑pravastatin  ↑rosuvastatin | Potentially increased concentrations. | **ELIGIBLE** – advise to monitor for side effects. |
| Microsomal triglyceride transfer protein (MTTP) inhibitor | ↑lomitapide | Increased plasma concentrations of lomitapide.  **Contraindicated.** | **NOT ELIGIBLE** |
| Migraine treatments | ↑eletriptan | Not recommended with strong 3A4 inhibitors.  **Contraindicated.** | **NOT ELIGIBLE** |
| Hormonal contraceptive | ↓ethinyl estradiol | Ritonavir may reduce ethinyl estradiol concentrations and change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives. | **Potentially ELIGIBLE** if willing to use an additional barrier method during treatment with Paxlovid™, and until one full menstrual cycle after stopping Paxlovid™. |
| Immunosuppressants | ↑cyclosporine  ↑tacrolimus  ↑everolimus  ↑sirolimus | Ritonavir is expected to increase the plasma concentrations of cyclosporine, tacrolimus, sirolimus or everolimus.  **Contraindicated.** | **NOT ELIGIBLE** |
| Phosphodiesterase (PDE5) Inhibitors | ↑ avanafil  ↑ vardenafil | Increased plasma concentrations of avanafil and vardenafil.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑sildenafil (Revatio®) used for pulmonary arterial hypertension (PAH) | Increased sildenafil concentrations can potentially result in visual abnormalities, hypotension, prolonged erection, and syncope.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑sildenafil for erectile  dysfunction | **Contraindicated.** | **NOT ELIGIBLE** |
| ↑tadalafil | **Contraindicated.** | **NOT ELIGIBLE** |
| Renin inhibitor | ↑aliskiren | Not recommended with a 3A4 and P-gp inhibitor.  **Contraindicated.** | **NOT ELIGIBLE** |
| Sedative/hypnotics | ↑clonazepam  ↑diazepam  ↑estazolam  ↑flurazepam  ↑oral and parenteral midazolam  ↑triazolam | Increased concentrations of can increase risk of extreme sedation and respiratory depression.  **Contraindicated.** | **NOT ELIGIBLE** |
| ↑alprazolam  ↑buspirone | Potentially increased concentrations of alprazolam and buspirone. | **ELIGIBLE** – but  advise to monitor for side effects and drowsiness. |
| Sleeping agent | ↑zolpidem | Zolpidem & ritonavir may be co-administered with careful  monitoring for excessive sedative effects. | **ELIGIBLE** – but  advise to monitor for side effects and drowsiness. |
| Smoke cessation | ↓bupropion | Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. Effects may not be seen with the short course of Paxlovid™. | **ELIGIBLE** |
| Steroids | Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone | Systemic corticosteroid effects have been reported in patients receiving long-term ritonavir and inhaled or intranasal fluticasone propionate. Given the short course of Paxlovid™ this risk is considered to be low. | **ELIGIBLE** |
| ↑dexamethasone  ↑prednisolone | Ritonavir is expected to increase concentrations of dexamethasone and prednisolone. However, given the short duration of Paxlovid™ treatment, this risk is considered to be low. | **ELIGIBLE** |
| Thyroid hormone replacement therapy | levothyroxine (no interaction expected) | Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Given the short duration of Paxlovid™ treatment, this risk is considered to be low. | **ELIGIBLE** |