Nirmatrelvir/Ritonavir (Paxlovid®). Utilización en COVID-19

(Documento actualizado el 02/11/2022)

Antes de prescribir Paxlovid®, se recomienda hacer una valoración individual del beneficio-riesgo del tratamiento, debido a las incertidumbres sobre su efectividad en este momento y a la complejidad clínica del manejo de las interacciones farmacológicas, así como consensuar su uso con el paciente tras una información adecuada.

Paxlovid® consta de 2 medicamentos incluidos en el mismo envase:

- **Nirmatrelvir** es un inhibidor de la proteasa SARS-CoV-2 3CL, que en última instancia hace que la replicación viral se detenga (comprimido rosa).
- **Ritonavir** es un potente inhibidor de CYP3A4. No es activo contra el SARS-CoV-2. Se administra como potenciador farmacocinético para retardar el metabolismo de nirmatrelvir, aumentando así las concentraciones de nirmatrelvir. Es causante de múltiples interacciones con otras sustancias.

Indicaciones

Paxlovid® está indicado en el tratamiento de la enfermedad por coronavirus 2019 (Covid-19) en adultos que no requieren aporte de oxígeno suplementario y que **tienen un riesgo alto de progresar a Covid-19 grave**:

Condiciones de alto riesgo priorizadas por el Sistema Nacional de Salud [1] (versión 7 AEMPS - 02/11/2022)

1. Personas inmunocomprometidas y con otras condiciones de alto riesgo, independientemente del estado de vacunación:

- Receptores de trasplante de progenitores hematopoyéticos o CAR-T, en los dos años tras el trasplante/tratamiento, en tratamiento inmunosupresor o que tengan EICH independientemente del tiempo desde el TPH.
- Receptores de trasplante de órgano sólido (menos de dos años o sometido a tratamiento inmunosupresor por sospecha de rechazo activo con independencia del tiempo desde el trasplante).
- Inmunodeficiencias primarias: combinadas y de células B en las que se haya demostrado ausencia de respuesta vacunal.
- Tratamiento activo con quimioterapia mielotóxica para enfermedades oncológicas o hematológicas. Se excluye el uso de hormonoterapia, inhibidores de checkpoint inmunes u otros tratamientos que no condicionan aumento en el riesgo de infección (por ejemplo, anticuerpos monoclonales antidiana no mielotóxicos).
- Pacientes con tratamientos onco-hematológicos no citotóxicos con neutropenia (< 500 neutrófilos/mcL) o linfopenia (< 1000 linfocitos/mcL) en el momento de la infección.
- Infección por VIH con ≤200 cel/ml (analítica en los últimos 6 meses).
- Fibrosis quística.
- Síndrome de Down con 40 o más años de edad (nacidos en 1981 o antes).
- Tratamiento inmunosupresor con corticoides orales a altas dosis o durante tiempo prolongado y ciertos inmunomoduladores no biológicos:
  - Tratamiento con corticoides orales a altas dosis de manera continuada (equivalente a ≥20 mg/día de prednisolona durante 10 o más días consecutivos en los treinta días previos.
  - Tratamiento prolongado con corticoides orales a dosis moderadas (equivalente a ≥10 mg/día de prednisolona durante más de cuatro semanas consecutivas en los treinta días previos).
  - Altas dosis de corticoides orales (equivalente a >40mg/día de prednisolona durante más de una semana) por cualquier motivo en los treinta días previos.
  - Tratamiento en los tres meses anteriores con fármacos inmunomoduladores no biológicos, como metotrexato (>20 mg/semana o >15 mg/m2/sem, oral o subcutáneo), leflunomida, 6 mercaptopurina (>1,5 mg/kg/día) o azatioprina (>3 mg/kg/día), ciclosporina, micofenolato, tacrolimus y sirolimus en los tres meses previos
- Tratamiento inmunosupresor con inmunomoduladores biológicos: personas que han recibido en los tres meses anteriores (seis meses en caso de anti CD20) terapia específica con alguno de los fármacos de los siguientes grupos:
  - Anticuerpos monoclonales anti CD20
  - Inhibidores de la proliferación de células B
  - Proteínas de fusión supresoras de linfocitos T
  - Inhibidores de la interleukina 1 (IL-1)
  - Anticuerpos monoclonales anti-CD52
  - Moduladores del receptor de la esfingosina-1-fosfato
  - Inhibidores de la proteinquinasa.
  - Inhibidores de la familia janus quinasa (JAK)

2. Personas NO vacunadas [2] > 80 años

3. Personas NO vacunadas [2] > 65 años y con al menos 1 factor de riesgo para progresión.

4. Personas vacunadas (hace más de 6 meses) con > 65 años y con al menos 1 factor de riesgo para progresión

Se consideran **factores de riesgo de progresión:**

- Enfermedad renal crónica: pacientes con estadios de enfermedad renal crónica 3b (tasa de filtración glomerular inferior a 60 ml/min).
- Enfermedad hepática crónica: pacientes con una clasificación en la escala de Child-Pugh para gravedad de la enfermedad hepática de clase B (enfermedad hepática descompensada).
- Enfermedad neurológica crónica (esclerosis múltiple, esclerosis lateral amiotrófica, miastenia gravis o enfermedad de Huntington).
- Enfermedades cardiovasculares, definidas como antecedentes de cualquiera de los siguientes: infarto de miocardio, accidente cerebrovascular (ACV), accidente isquémico transitorio (AIR), insuficiencia cardíaca, angina de pecho con nitroglicerina prescrita, injertos de revascularización coronaria, intervención coronaria percutánea, endarterectomía carotídea y derivación aórtica.
- Enfermedad pulmonar crónica (EPOC de alto riesgo (FEV1 postbroncodilatación < 50% o disnea (mMRC) de 2-4 o 2 o más exacerbaciones en el último año o 1 ingreso); asma con requerimiento de tratamiento diario).
- Diabetes con afectación de órgano diana.
- Obesidad (IMC ≥ 35)
- Bajo peso (IMC ≤ 18,5)

[1] Excluidos, por estar contraindicados con Paxlovid®, la condición de alto riesgo "Tratamiento sustitutivo renal (hemodiálisis y diálisis peritoneal)" y los factores de riesgo referidos a enfermedad renal crónica 4-5 (tasa de filtración glomerular < 30 ml/min) y enfermedad hepática crónica clase C.

[2] Personas que no han recibido la pauta de vacunación completa, incluidas las dosis de recuerdo y no han padecido la enfermedad en los 3 últimos meses.

Los pacientes con enfermedad leve-moderada que presenten las condiciones de alto riesgo descritas (apartado 1), pueden ser candidatos tanto a anticuerpos monoclonales (en pacientes con serología negativa o con bajo nivel de protección) como a antivirales (sin considerar serología). Sin embargo, se considera que la **primera opción terapéutica recomendada es Paxlovid** en pauta de 5 días.

En el caso de los pacientes incluidos en el apartado 1 que no sean candidatos a Paxlovid, si se dispone de resultado serológico que muestre que no hay respuesta a la vacunación (serología negativa o nivel de protección bajo) puede considerarse la administración de anticuerpos monoclonales.

En el resto de los casos (apartado 1 si no se dispone de serología o se ha confirmado una respuesta positiva a la vacuna, así como los apartados 2, 3 y 4), se puede considerar como alternativa el uso de:

- Veklury® (remdesivir) en pauta de 3 días. Se debe iniciar el tratamiento dentro de los 7 días de evolución.
- Lagevrio® (molnupiravir), en pauta de 5 días. Iniciar tratamiento dentro de los 5 días de evolución.

(ver AEMPS v7)

Posología

Paxlovid® se debe administrar lo antes posible tras el diagnóstico de COVID-19 y dentro de los 5 días posteriores al inicio de los síntomas.

La dosis recomendada es de 300 mg de nirmatrelvir (2 comprimidos rosas de 150 mg) con 100 mg de ritonavir (un comprimido blanco de 100 mg), en total 3 comprimidos tomados juntos por vía oral cada 12 horas. Es decir 6 comprimidos al día, durante 5 días. Cada envase contiene 5 blíster, cada blíster el tratamiento para un día.

Consideraciones especiales de dosificación

En pacientes con alteración de función renal moderada (TFG entre 30-60 mL/min), hay que **reducir la dosis** a 150 mg de nirmatrelvir (1 comprimido) y mantener los 100 mg de ritonavir (1 comprimido) tomados juntos cada 12 horas. Es decir, 2 comprimidos cada 12 horas durante 5 días. Sobrarían 10 comprimidos rosas por cada envase.

Eficacia

Es necesario tener en cuenta que en el ensayo clínico pivotal EPIC-HD sólo se incluyeron pacientes no vacunados frente al SARS-CoV-2, por lo que la eficacia observada del tratamiento con Paxlovid® no sería directamente extrapolable a la población española, con una tasa de vacunación superior al 90%.

A pesar de excluir en el ensayo tanto a pacientes vacunados como a pacientes que habían pasado la enfermedad, aproximadamente la mitad de ellos (51,2%) tuvo serología positiva para el SARS-CoV2 y la eficacia en estos pacientes fue unas 10 veces menor que en aquellos con serología negativa. En pacientes seronegativos, la diferencia absoluta en el número de ingresos o muerte fue del 10,25% (1,4% con Paxlovid *vs* 11,5% placebo), mientras que en pacientes seropositivos la diferencia fue del 1,34% (0,2% con Paxlovid *vs* 1,5% con placebo).

Esto se puede traducir en que los pacientes más beneficiados por el tratamiento son los seronegativos, ya que para evitar un ingreso/muerte entre pacientes seronegativos habría que tratar a 10 (IC95%: 8 a 14) pacientes mientras que para conseguir el mismo resultado entre pacientes seropositivos habría que tratar a 75 (IC95%: 41 a 435) pacientes.

	Variable principal: Proporción de pacientes con hospitalización por COVID-19 o muerte por cualquier causa (hasta el día 28).					
	Paxlovid®		**Placebo**		Reducción absoluta del riesgo con respecto a placebo* [IC95%]	NNT [IC95%]
	Nª de Pacientes	Incidencia acumulada (%)	Nª de Pacientes	Incidencia acumulada (%)		
Serología Negativa	487	7 (1,4%)	505	58 (11,5%)	-10,25% (-13,2% a -7,21%)	10 (8 a 14)
Serología positiva	540	1 (0,2%)	528	8 (1,5%)	-1,34% (-2,45% a -0,23%)	75 (41 a 435)
Total	**1039**	**8 (0,8%)**	**1046**	**66 (6,3%)**	**-5,6% (-7,2% a -4%)**	**18 (14 a 25)**
Limitaciones: • NNT en pacientes con anticuerpos basales para COVID-19: 75 (41 a 435) vs 10 (8 a 14) en seronegativos. • Faltan datos sobre la actividad del antiviral frente a la variante ómicron, ya que el 98% de los pacientes presentaban la variante delta. • Edad media de la población: 44 años. Población > 60 años (16,1% grupo Paxlovid® y 21,4% grupo de placebo).						

Tabla tomada de: Ficha Paxlovid® BITn Servicio Navarro de Salud. Osasunbidea y ficha técnica de Paxlovid®

Seguridad: interacciones

Interacciones de nirmatrelvir/ritonavir

El ritonavir es un potente inhibidor de la isoenzima CYP3A4 y de varios transportadores de fármacos (p. ej., glicoproteína P). El inicio de la inhibición de ritonavir es rápido. El máximo se alcanza a las 48 horas y tarda unos días (2-3) en disiparse después de completar la terapia.

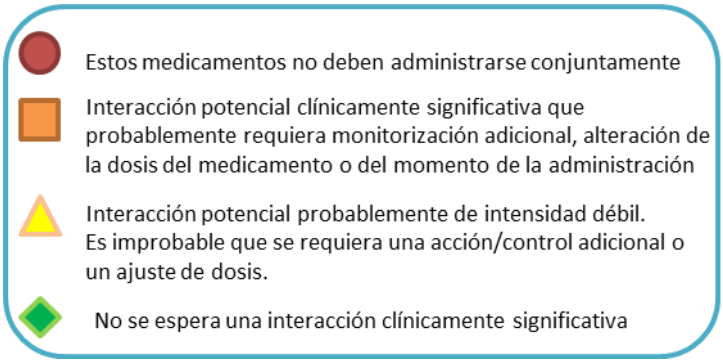
Tanto ritonavir como nirmatrelvir son sustratos de CYP3A4.

Nirmatrelvir/ritonavir está contraindicado en pacientes que toman medicamentos que son:

- Altamente metabolizados por CYP3A4, donde las concentraciones elevadas pueden poner en peligro la vida.
- Inductores potentes de CYP3A4 que pueden reducir la eficacia de nirmatrelvir/ritonavir y contribuir al desarrollo de resistencia a los medicamentos.

Antes de prescribir el tratamiento es necesaria una valoración de toda la medicación o suplementos que tome el paciente para evitar toxicidades, en ocasiones graves. El manejo de estas interacciones puede ser complejo y se recomienda que se obtenga información de la ficha técnica y también de la página de la Universidad de Liverpool en https://www.covid19-druginteractions.org/checker (ver manual de uso en anexo I)

Esta página utiliza un código de colores para clasificar las interacciones



Medicación contraindicada

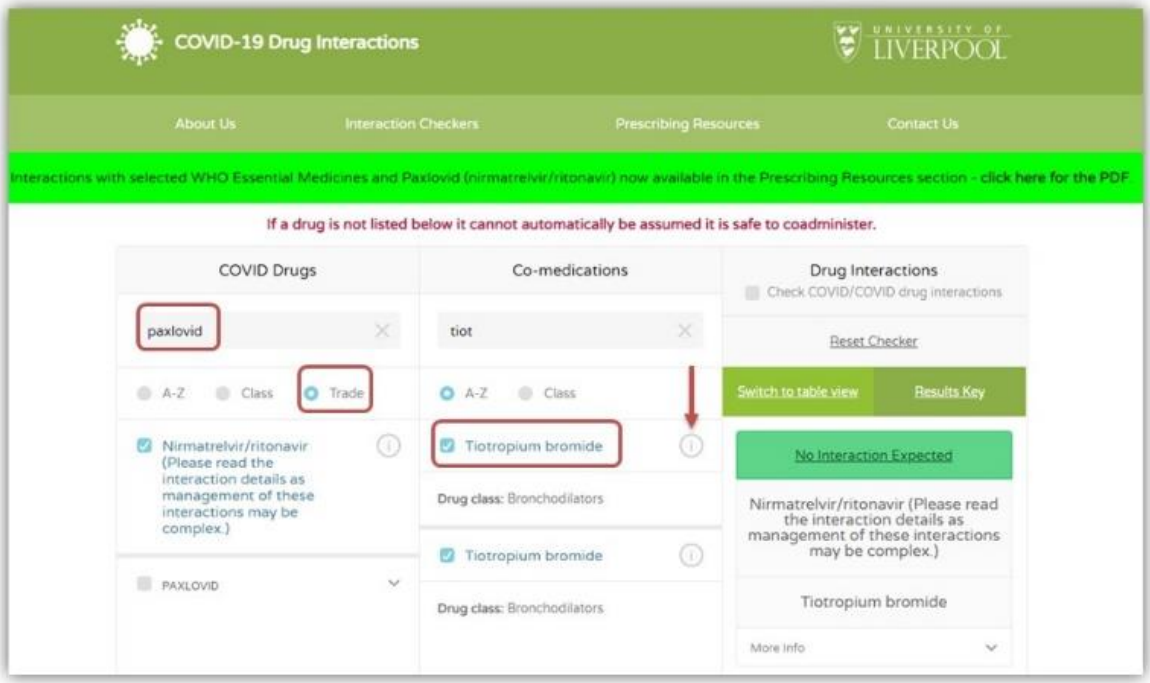
- Si el paciente **está tomando o ha tomado un inductor de la enzima CYP3A4 en los últimos 14 días** (p. ej., ciertos anticonvulsivos: antineoplásicos, rifampicina, hierba de San Juan):
  NO prescribir nirmatrelvir/ritonavir.
- Si el paciente toma un fármaco que interactúa con una vida media plasmática prolongada y una ventana terapéutica estrecha (p. ej., ciertos antiarrítmicos, antipsicóticos, antineoplásicos), el fármaco que interactúa persistirá en el cuerpo después de la última dosis y aún puede interactuar con nirmatrelvir/ritonavir: NO prescribir nirmatrelvir/ritonavir incluso si se puede suspender el fármaco que interactúa o si no han transcurrido más de 14 días desde su administración.
- Si el paciente toma un fármaco que interactúa y que se puede suspender, suspenda el fármaco a partir del primer día de terapia con nirmatrelvir/ritonavir, y reanude de 3 a 5 días después de la última dosis de nirmatrelvir/ritonavir, dependiendo de cada caso.

Interacción potencial clínicamente significativa

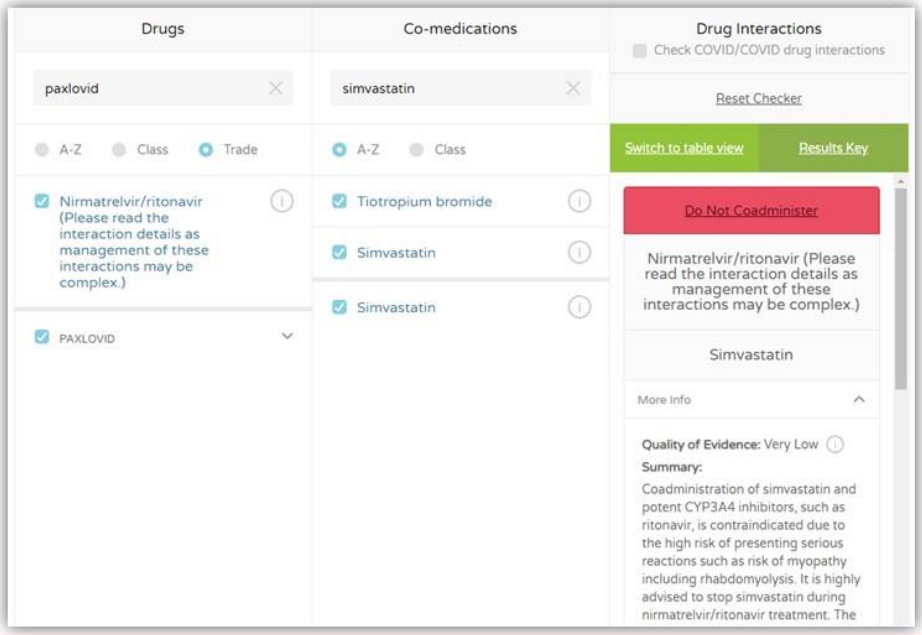
En algunos casos es posible ajustar la dosis o el intervalo de dosificación, reemplazar el medicamento por otro alternativo, manejar los efectos adversos y guiar la monitorización terapéutica de fármacos.

Se recomienda consultar la información actualizada, antes de la prescripción o en el proceso de validación, mediante la página web Interaction Checker y la tabla de interacciones entre Nirmatrelvir/Ritonavir y medicamentos esenciales (Anexo II) de la Universidad de Liverpool, y el apéndice de interacciones de la Universidad de Waterloo (Ontario) (Anexo III)

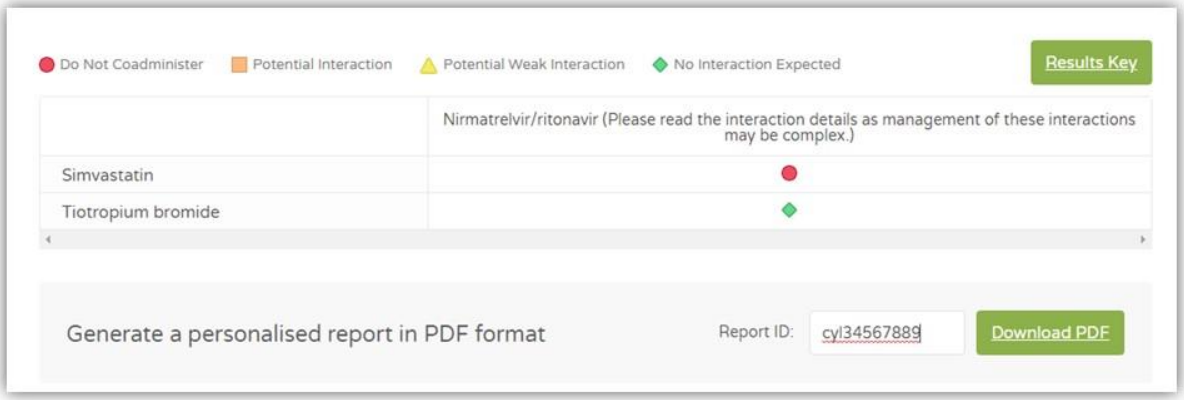
Anexo I. Manual de Interaction checker - Universidad de Liverpool



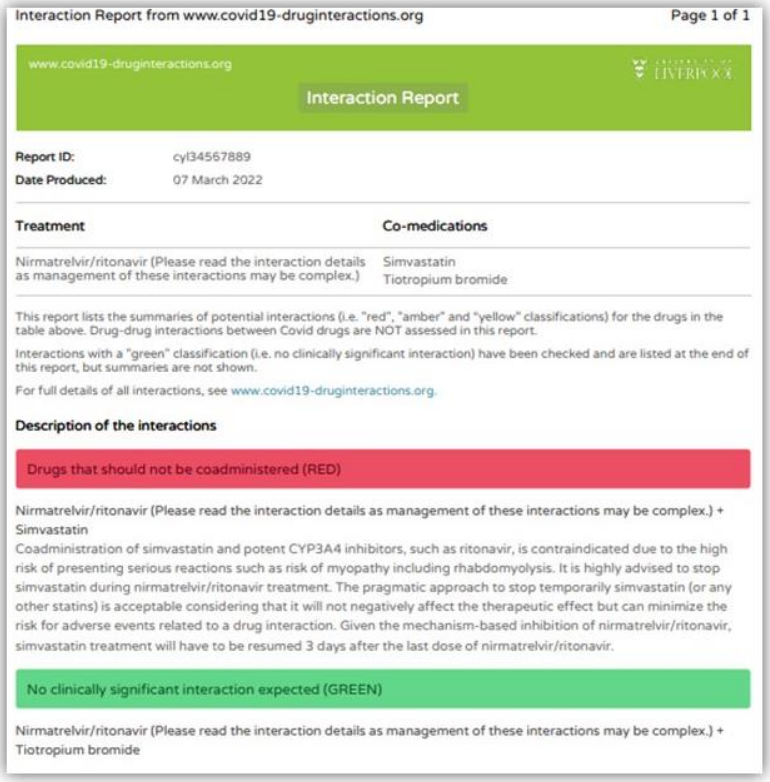
- Seleccionar en *Drugs paxlovid* ,nombre comercial (*Trade*)
- Añadir los otros medicamentos en comedicación (principio activo)
- Desplegar (i)



- Se pueden añadir otros medicamentos, en este ejemplo simvastatina.
- El sistema informa la contraindicación en rojo.
- Si se despliega "More information" se detalla el tipo de interacción y si existe alguna posibilidad de actuación (suspender, cambios de dosis…)
- Se puede clicar en "Results Key" y se despliega el resultado para todos los medicamentos consultados



- *"Results Key"* devuelve el listado de la interacción consultada para cada medicamento con la clave de colores.
- *"Personalized report":* se puede generar un informe que recoge las información asociada a cada interacción. En *Report ID* se puede teclear el CIP del paciente y generar el informe.



Interaction Report from www.covid19-druginteractions.org Page 1 of 1

www.covid19-druginteractions.org

Interaction Report

Report ID: cyl34567889
Date Produced: 07 March 2022

Treatment	Co-medications
Nirmatrelvir/ritonavir (Please read the interaction details as management of these interactions may be complex.)	Simvastatin Tiotropium bromide

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above. Drug-drug interactions between Covid drugs are NOT assessed in this report.

Interactions with a "green" classification (i.e. no clinically significant interaction) have been checked and are listed at the end of this report, but summaries are not shown.

For full details of all interactions, see www.covid19-druginteractions.org.

Description of the interactions

Drugs that should not be coadministered (RED)

Nirmatrelvir/ritonavir (Please read the interaction details as management of these interactions may be complex.) + Simvastatin

Coadministration of simvastatin and potent CYP3A4 inhibitors, such as ritonavir, is contraindicated due to the high risk of presenting serious reactions such as risk of myopathy including rhabdomyolysis. It is highly advised to stop simvastatin during nirmatrelvir/ritonavir treatment. The pragmatic approach to stop temporarily simvastatin (or any other statins) is acceptable considering that it will not negatively affect the therapeutic effect but can minimize the risk for adverse events related to a drug interaction. Given the mechanism-based inhibition of nirmatrelvir/ritonavir, simvastatin treatment will have to be resumed 3 days after the last dose of nirmatrelvir/ritonavir.

No clinically significant interaction expected (GREEN)

Nirmatrelvir/ritonavir (Please read the interaction details as management of these interactions may be complex.) + Tiotropium bromide

Personalized report

Este informe puede ser útil para, simplemente, documentar la validación, trasladar al prescriptor o consultar a un especialista si se necesita

ANEXO II. Interacciones con medicamentos esenciales-U. Liverpool (sep 2022)

Liverpool Drug Interactions Group

University of Liverpool

Interactions with Essential Medicines & Nirmatrelvir/ritonavir (NMV/r)

Charts revised 16 September 2022 — *Page 1 of 2*

Please check www.covid19-druginteractions.org for updates.

Interaction tables - refer to page 2 for legend, abbreviations and notes

Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister.
Drug interaction data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.
Management of interactions with nirmatrelvir/ritonavir (Paxlovid) may be complex and full details should be obtained from the website where possible.

Analgesics	
	Codeine
	Diclofenac
☐	Fentanyl
	Hydromorphone
	Ibuprofen
	Mefenamic acid
	Morphine
☐	Oxycodone
	Paracetamol
	Tramadol
Antiarrhythmics	
!	Amiodarone
☐	Digoxin
☐	Lidocaine
Antibacterials	
	Amikacin
	Amoxicillin
	Ampicillin
☐	Bedaquiline
	Cefalexin
	Cefazolin
	Cefixime
	Cefotaxime
	Ceftriaxone
	Chloramphenicol
	Ciprofloxacin
	Clarithromycin (a)
	Clindamycin
	Clofazimine
	Cloxacillin
	Cycloserine
	Dapsone
☐	Delamanid
	Doxycycline
☐	Erythromycin
	Ethambutol
	Ethionamide
	Gentamicin
	Imipenem/cilastatin
	Isoniazid
	Kanamycin
	Levofloxacin
	Linezolid
	Meropenem
	Metronidazole
	Moxifloxacin
	Nitrofurantoin
	Ofloxacin
	Para-aminosalicylic acid
	Penicillins
	Piperacillin
	Pyrazinamide
☐	Rifabutin (b)
✖	Rifampicin
✖	Rifapentine
	Spectinomycin
	Streptomycin
	Sulfadiazine
	Tazobactam
	Tetracyclines
	Trimethoprim/ sulfamethoxazole
	Vancomycin

Anticoagulants/antiplatelets	
☐	Apixaban
	Aspirin (antiplatelet)
	Clopidogrel (stented) (c)
☐	Dabigatran (d)
	Dalteparin
☐	Edoxaban (e)
	Enoxaparin
	Heparin
	Rivaroxaban
	Streptokinase
☐	Warfarin
Anticonvulsants	
✖	Carbamazepine
	Clonazepam
☐	Ethosuximide
	Lamotrigine
✖	Phenobarbital
✖	Phenytoin
	Sodium valproate
	Valproate semisodium (Divalproex sodium)
	Valproic acid
Antidepressants	
	Amitriptyline
	Clomipramine
	Fluoxetine
	Lithium
✖	St John's Wort
Antidiabetics	
	Glibenclamide
	Gliclazide
	Insulin
	Metformin
Antifungals	
	Amphotericin B
	Fluconazole
	Flucytosine
	Griseofulvin
	Itraconazole (f)
	Ketoconazole (f)
	Nystatin
☐	Voriconazole
Antimalarials	
☐	Amodiaquine
	Artemether
	Artesunate
	Atovaquone
	Lumefantrine
☐	Mefloquine
☐	Piperaquine
	Primaquine
	Proguanil
☐	Quinine
Antipsychotics	
	Chlorpromazine
	Clozapine
	Fluphenazine
☐	Haloperidol
☐	Risperidone

Anxiolytics	
	Diazepam
	Lorazepam
	Midazolam
Beta blockers	
	Atenolol
	Bisoprolol
	Carvedilol
	Metoprolol
	Propranolol
Bronchodilators	
	Aminophylline
	Ipratropium bromide
	Salmeterol
Calcium channel blockers	
	Amlodipine
	Nifedipine
	Verapamil
Cancer drugs	
☐	Dasatinib (g)
☐	Erlotinib (h)
☐	Imatinib (i)
	Methotrexate
☐	Vinblastine (j)
Contraceptives	
	Ethinylestradiol
	Etonogestrel (IMP)
	Etonogestrel (VR)
	Levonorgestrel (COC)
	Levonorgestrel (EC)
	Levonorgestrel (IUD)
	Levonorgestrel (POP)
	Medroxyprogesterone (depot injection)
	Norethisterone (COC)
	Norethisterone (IM)
	Norethisterone (POP)
	Norgestrel (COC)
COVID19 therapies	
	Budesonide (inhaled)
	Convalescent plasma
	Dexamethasone
	Hydrocortisone
	Infliximab
	Methylprednisolone
	COVID19 vaccines
Gastrointestinal agents	
☐	Aprepitant
	Domperidone
	Lactulose
	Loperamide
	Mesalazine
	Metoclopramide
	Omeprazole
	Ondansetron
	Ranitidine
	Senna
HCV antivirals	
	Glecaprevir/pibrentasvir
	Ledipasvir/sofosbuvir
	Ombitasvir/paritaprevir/r
	Sofosbuvir/velpatasvir

Herbals/supplements	
	Folic acid
	Magnesium
✖	St John's Wort
HIV antiretrovirals	
	Abacavir
	Atazanavir/ritonavir
	Darunavir/ritonavir
	Dolutegravir
	Efavirenz
	Emtricitabine
	Lamivudine
	Lopinavir/ritonavir
	Nevirapine
	Raltegravir
	Tenofovir alafenamide
	Tenofovir-DF
	Zidovudine
Hypertension/heart failure	
	Amiloride
	Dopamine
	Enalapril
	Furosemide
	Hydrochlorothiazide
	Isosorbide dinitrate
	Lisinopril
	Losartan
	Methyldopa
	Spironolactone
Immunosuppressants	
	Azathioprine
	Ciclosporin (k)
	Everolimus
Lipid lowering agents	
☐	Atorvastatin
	Fluvastatin
	Lovastatin
	Simvastatin
Others	
	Allopurinol
	Ergometrine
	Ergotamine
	Levodopa
	Levothyroxine
Steroids	
	Beclometasone
	Betamethasone
	Fludrocortisone
	Prednisolone
	Testosterone
☐	Triamcinolone

Liverpool Drug Interactions Group — University of Liverpool

Interactions with Essential Medicines & Nirmatrelvir/ritonavir (NMV/r)

Charts revised 16 September 2022 — *Page 2 of 2*

Please check www.covid19-druginteractions.org for updates.

Legend

Colour/Symbol		Recommendation for NMV/r use
!	**Do not co-administer**	**Do not use NMV/r ⇒ alternative COVID-19 therapy** Risk of serious toxicity. Stopping the drug does not mitigate the interaction due to its prolonged half-life.
✖	**Do not co-administer**	**Do not use NMV/r ⇒ alternative COVID-19 therapy** Strong inducer can jeopardize NMV/r efficacy due to persisting induction after stopping the drug.
	Do not co-administer	**NMV/r use ONLY possible if drug is paused or replaced by a non-interacting drug** Risk of serious toxicity. Only start NMV/r if the drug can be safely paused or replaced. Drug can be resumed at least 3 days (if possible, up to 5 days for narrow therapeutic index drugs) after completing NMV/r therapy.
☐	**Potential interaction** **Dose adjustment and/or close monitoring required.**	**Stop or replace drug if possible or consult specialist for dose adjustment/monitoring to allow use with NMV/r** Ideally, only start NMV/r if the drug can be safely paused or replaced. Alternatively, dose adjust/monitor. Refer to www.covid19-druginteractions.org for detailed information.
	Potential interaction **Manageable by counselling patient**	**Proceed with NMV/r** Interaction manageable by counselling the patient about potential interaction and advising to temporarily stop the drug if feeling unwell.
	Weak interaction **No action needed**	**Proceed with NMV/r** Drug metabolized partially by CYP3A4 or with low risk of adverse event from interaction.
	No interaction expected	**Proceed with NMV/r**

Contraceptive Abbreviations

COC = combined oral contraceptive
EC = emergency contraception
IUD = intrauterine device
IM = intramuscular
IMP = implant
POP = progestin only contraceptive pill
VR = vaginal ring

Notes

a No dose reduction or monitoring in patients with normal renal function.

b Rifabutin dosed 150 mg once daily with NMV/r.

c Ritonavir decreases clopidogrel efficacy therefore NMV/r cannot be prescribed in high risk situation (i.e. initial period (at least 6 weeks) post coronary stenting). NMV/r is allowed if clopidogrel is used outside this period or if clopidogrel is used as alternative to aspirin (intolerant patients).

d When used for the treatment of atrial fibrillation, reduce dabigatran to 110 mg twice daily in individuals with normal renal function and to 75 mg twice daily in individuals with moderate renal impairment. Consult www.covid19-druginteractions.org for management in other indications.

e When used for the treatment of atrial fibrillation, reduce edoxaban to 30 mg. Consult www.covid19-druginteractions.org for management in other indications.

f Itraconazole or ketoconazole should not be used at doses >200 mg/day.

g The decision to pause or dose adjust dasatinib should be made in conjunction with the patient's oncologist.
Chronic phase chronic myelogenous leukaemia: pause dasatinib and restart 3 days after completing NMV/r. Alternatively, consider reducing dasatinib dose to 20 mg (in patients receiving 100 mg daily) or 40 mg (in patients receiving 140 mg daily) and monitor for toxicity.
Accelerated or blast phase chronic myelogenous leukaemia: do not coadminister, use alternative COVID-19 therapy.

h The decision to pause or dose adjust erlotinib should be made in conjunction with the patient's oncologist.
If it is decided to pause treatment, restart erlotinib 3 days after completing NMV/r treatment. If pausing erlotinib treatment is not feasible, continue full dose erlotinib with patient self-monitoring for rash and diarrhoea. If these do occur, reduce erlotinib dose in 50 mg decrements or re-assess for a short pause.

i The decision to pause imatinib should be made in conjunction with the patient's oncologist. If it is decided to hold treatment, restart imatinib 3 days after completing NMV/r treatment. Alternatively, imatinib may be coadministered with monitoring for adverse effects (fluid retention, nausea and neutropenia). NMV/r is expected to have a modest effect on imatinib exposure. Coadministration with ritonavir (600 mg once daily) for 3 days did not significantly alter imatinib exposure (*van Erp NP et al. Clin Cancer Res. 2007;13(24):7394-400*).

j The decision to pause or dose adjust vinblastine should be made in conjunction with the patient's oncologist. Vinblastine may be paused in the context of acute infection. Restart vinblastine 3 days after completing NMV/r treatment. Alternatively, vinblastine may be coadministered with close monitoring for haematologic toxicity and neurotoxicity. Some providers may wish to empirically reduce vinblastine dose, especially in patients who have previously experienced or are at high risk for toxicity.

k The management of this interaction is challenging and would require dosage adjustment and therapeutic drug monitoring (TDM) of ciclosporin which may not be possible given the short duration of NMV/r treatment. An alternative COVID treatment should be considered. However, if TDM is available, an empiric dose reduction of ciclosporin has been suggested (reduce total daily dose by 80% and administer once daily) during treatment with NMV/r (days 1-5). Ciclosporin concentrations should be assessed on day 6 or 7 and repeated every 2-4 days.

ANEXO III. Apéndice de interacciones de la Universidad de Waterloo (sep 2022)

June 6, 2022

Appendix: Nirmatrelvir/ritonavir (*Paxlovid*) Drug Interactions

June 6, 2022. This document will be updated as more information becomes available.

Guiding principles for managing drug interactions categorized as ● and ◆.

There is limited drug interaction data for nirmatrelvir/ritonavir (which is a potent CYP3A4/P-glycoprotein inhibitor). Most potential interactions listed below are based on known/anticipated effects with ritonavir alone or with other protease inhibitors. In some instances, pharmacokinetic interaction data for other potent CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) are included in this table to help predict the potential extent of an interaction effect with nirmatrelvir/ritonavir.

General recommendation: ● ◆

Hold the interacting drug for one week (i.e., beginning on the first day of nirmatrelvir/ritonavir and resuming two days after completing nirmatrelvir/ritonavir).

› *Ritonavir inhibition is not immediately reversible.*

If holding a drug for one week is not a safe option:

- Use an alternative COVID-19 agent for ● drugs, or;
- Consider therapy modification for ◆ drugs.

Caution: ⚠

Some drugs may need to be held longer due to a greater sensitivity to ritonavir inhibition (e.g., calcineurin inhibitors).

In many instances, replacing a drug is not feasible, and may introduce more risk of harm or error (e.g., patient takes both the held and new drug, forgets to restart original drug, etc).

› Recommendations in this appendix are based on Canadian product monographs, the Liverpool COVID-19 Drug Interactions Database (University of Liverpool, 2022), Lexi-Interact Online Database (Hudson OH, Wolters Kluwer, 2022), and additional references as noted.

Disclaimer

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Neither the Ontario COVID-19 Science Advisory Table, the University of Waterloo, nor the authors and their respective institutions are responsible for deletions or inaccuracies in information or for claims of injury resulting from any such deletions or inaccuracies. Mention of specific drugs, drug doses, or drug combinations within this document does not constitute endorsement by the Ontario COVID-19 Science Advisory Table, the University of Waterloo, or the authors and their respective institutions.

This document is intended to complement (but is separate from) the Ontario COVID-19 Science Advisory Table Drugs and Biologics Clinical Practice Guidelines.

	Drug	Recommendation	Comments
◆	Abemaciclib (*Verzenio*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, for patients who have not previously had dose reduction for toxicity, consider a dose reduction to 50 mg once daily with close monitoring for toxicity.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Cyclin-dependent kinase inhibitors are generally held for acute infection. Abemaciclib AUC increased over 3-fold when coadministered with clarithromycin.
●	Alfuzosin (*Xatral*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, may consider giving every other day in patients with heightened risk of urinary retention. Monitor for hypotension.	Alfuzosin AUC increased 3-fold when coadministered with ketoconazole 400 mg.
◆	Alprazolam (*Xanax*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce alprazolam dose by at least 50% and monitor for increased effects.	Alprazolam AUC increased 148% and half-life increased from 13 to 30 hours when coadministered with ritonavir 200 mg x 4 doses.
◆	Amlodipine (*Norvasc*)	Reduce amlodipine dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Amlodipine AUC increased 2-fold when coadministered with indinavir/ritonavir or paritaprevir/ritonavir.

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AUC = Area under the curve

June 6, 2022

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Drug	Recommendation	Comments
Apixaban (*Eliquis*)	If possible, use alternative COVID-19 agent. If not possible, ensure stable renal function, then: **A) If already on low dose (2.5 mg BID) apixaban, continue.** **B) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold apixaban. 12 hours after the last dose of apixaban, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmaltrevir/ritonavir. Restart apixaban 2 days after completing nirmatrelvir/ritonavir. ⚠ *High risk of clot:* Hold apixaban. 12 hours after the last dose of apixaban, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours if >90 kg; ◦ **Enoxaparin** 1 mg/kg every 12 hours (preferred) OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart apixaban 2 days after completing nirmatrelvir/ritonavir. **C) If atrial fibrillation:** Decrease apixaban to 2.5 mg BID. Resume usual dose 2 days after completing nirmatrelvir/ritonavir. See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf	Canadian monograph states that coadministration with ritonavir is contraindicated. However, US product monograph suggests to decrease 5 mg twice daily dose to 2.5 mg twice daily when combined with strong inhibitors of CYP3A4 and P-glycoprotein. Eliquis (U.S.) Prescribing Information. Accessed February 8, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf Observational data from Italy found a 70 to 490% increase in apixaban levels in combination with *antivirals* containing ritonavir in hospitalized patients. Testa S, Prandoni P, Paoletti O et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. *J Thromb Haemost.* 2020;18:1320–1323. https://doi.org/10.1111/jth.14871 ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome
Aripiprazole (*Abilify*), oral	Reduce aripiprazole oral dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, restlessness, and sedation.	Aripiprazole AUC increased almost 2-fold when coadministered with ketoconazole. No clinically relevant interaction expected with long-acting injection.
Atorvastatin	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce atorvastatin to 10 mg daily. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Atorvastatin AUC increased almost 6-fold when coadministered with lopinavir/ritonavir 400/100 mg twice daily.
Bosutinib (*Bosulif*)	Hold bosutinib and start nirmatrelvir/ritonavir 24 hours after the last bosutinib dose. Restart bosutinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Bosutinib AUC increased almost 9-fold when coadministered with ketoconazole.
Brexpiprazole (*Rexulti*)	Reduce brexpiprazole dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, restlessness, sedation.	Brexpiprazole AUC increased 97% when coadministered with ketoconazole.
Buspirone (*Buspar*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce buspirone dose to 2.5 mg daily if the usual dose is 20 to 30 mg/day.	Buspirone AUC increased 19-fold when coadministered with itraconazole 200 mg/day for 4 days.

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AUC = Area under the curve

June 6, 2022

Appendix (Page 3)

	Drug	Recommendation	Comments
◆	Ceritinib (*Zykadia*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing ceritinib dose by 33% and monitor for toxicity.	Canadian monograph recommends to avoid concomitant use. However, US monograph suggests reducing dose by 33%, rounded to nearest 150 mg dosage strength. Zykadia (U.S.) Prescribing Information. Accessed February 8, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205755s016lbl.pdf Decision to hold or dose-adjust ceritinib should be made in conjunction with the patient's oncologist. Ceritinib AUC increased 3-fold when single dose coadministered with ketoconazole.
●	Cisapride	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Potential for serious and/or life-threatening adverse effects, including cardiac arrhythmias.
●	Clonazepam	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
◆	Clopidogrel (*Plavix*)	**Acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI):** • **If <1 month since ACS:** Use alternative COVID-19 agent. • **If <3 months since ACS or <1 month since PCI (no ACS):** Consider switching clopidogrel to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir; • **If >3 months since ACS or >1 month since PCI (no ACS):** Continue clopidogrel with acetylsalicylic acid (ASA) during nirmatrelvir/ritonavir therapy. If not taking ASA, consider switching to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir.	Coadministration will decrease the antiplatelet effect of clopidogrel. Clopidogrel active metabolite AUC decreased by 51 to 69% when coadministered with ritonavir.
●	Clorazepate	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
●	Cobimetinib (*Cotellic*)	Hold cobimetinib and start nirmatrelvir/ritonavir 24 hours after the last cobimetinib dose. Restart cobimetinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Cobimetinib AUC increased almost 7-fold when coadministered with ketoconazole.
●	Colchicine in renal/ hepatic Impairment	Coadministration is contraindicated in patients with renal and/or hepatic impairment. In patients with normal renal/hepatic function, colchicine may be administered at a lowered dose if practical: • **Treatment of gout flares:** 0.6 mg x 1 dose, then 0.3 mg (½ tablet) 1 hour later. Repeat dose no earlier than 3 days. • **Prevention of gout flares:** **a)** If on 0.6 mg twice daily: decrease to 0.3 mg once daily; **b)** If on 0.3 mg twice daily: decrease to 0.3 mg once every 2 days. • **Treatment of Familial Mediterranean fever:** maximum 0.6 mg (or 0.3 mg twice daily). In all cases, resume usual colchicine dose 2 days after completing nirmatrelvir/ritonavir.	Drug interaction could lead to potentially life-threatening/fatal adverse events.

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TIA = Transient ischemic attack
AUC = Area under the curve

June 6, 2022

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Drug	Recommendation	Comments
Cyclosporine (*Neoral*)	Reduce cyclosporine total daily dose by 80% and start nirmatrelvir/ritonavir 12 hours after the last cyclosporine dose. Continue at reduced dose throughout nirmatrelvir/ritonavir therapy. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be guided by therapeutic drug monitoring and in conjunction with the patient's transplant provider.	Check cyclosporine concentrations 2 days after the last dose of nirmatrelvir/ritonavir. • **If subtherapeutic:** increase cyclosporine dose. Consider resumption of twice daily dosing. • **If therapeutic:** continue with current cyclosporine dose. • **If supratherapeutic:** reduce or hold current cyclosporine dose. In all cases, repeat cyclosporine level in 2 to 4 days and continue to dose-adjust accordingly.
Dabigatran	If possible, use alternative COVID-19 agent. If not possible, then: **A) If already on low dose (110 mg BID) dabigatran, continue.** **B) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold dabigatran. 12 hours after the last dose of dabigatran, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmatrelvir/ritonavir. Restart dabigatran 2 days after completing nirmaltrevir/ritonavir. ⚠ *High risk of clot:* Hold dabigatran. 12 hours after the last dose of dabigatran, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours if >90 kg; ◦ **Enoxaparin** 1 mg/kg every 12 hours (preferred) OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart dabigatran 2 days after completing nirmatrelvir/ritonavir. **C) If atrial fibrillation:** Decrease dabigatran to 110 mg BID *(if eGFR>50 mL/minute)* OR decrease to 75 mg BID *(if eGFR 30-50 mL/minute)*. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Dabigatran AUC increased almost 2-fold when coadministered with nirmatrelvir/ritonavir. ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf
Dasatinib (*Sprycel*)	**Chronic phase chronic myelogenous leukemia (CML):** Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dasatinib dose to 20 to 40 mg and monitor for toxicity. **Accelerated or blast phase CML:** Do not coadminister; use alternate COVID-19 therapy.	Decisions to hold or dose-adjust dasatinib should be made in conjunction with the patient's oncologist. Dasatinib AUC increased 5-fold when coadministered with ketoconazole.
Dexamethasone, high dose	**High dose (≥20 mg daily):** Reduce dexamethasone dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. **Low dose (<20 mg daily):** Continue with usual dose during nirmatrelvir/ritonavir.	Dexamethasone AUC increased almost 3-fold when coadministered with voriconazole. Li M, Zhu L, Chen L et al. Assessment of drug-drug interactions between voriconazole and glucocorticoids. *J Chemother.* 2018;30(5):296-303. doi: 10.1080/1120009X.2018.1506693. Potential for risk of dexamethasone toxicity with high doses (≥20 mg daily). Clinically significant interaction is not expected with dexamethasone at low doses, including when used for COVID-19 treatment.

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AUC = Area under the curve

June 6, 2022

Appendix (Page 5)

	Drug	Recommendation	Comments
●	Diazepam (*Valium*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
◆	Digoxin	Reduce digoxin dose by 50% OR hold and restart 2 days after completing nirmatrelvir/ritonavir.	
◆	Diltiazem (*Tiazac, Cardizem*)	Reduce diltiazem dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor heart rate and blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.
●	Dofetilide	If possible, use alternative COVID-19 agent. Alternatively, hold dofetilide and restart 2 days after completing nirmatrelvir/ritonavir.	Dofetilide is metabolized to a small extent through CYP3A4.
◆	Edoxaban (*Lixiana*)	If possible, use alternative COVID-19 agent. If not possible, ensure stable renal function, then: **A) If already on low dose (30 mg once daily) edoxaban, continue.** **B) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold edoxaban. 24 hours after the last dose of edoxaban, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmaltrevir/ritonavir. Restart edoxaban 2 days after completing nirmatrelvir/ritonavir. ⚠ *High risk of clot:* Hold edoxaban. 24 hours after the last dose of edoxaban, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours if >90 kg; ◦ **Enoxaparin** 1 mg/kg every 12 hours (preferred) OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart edoxaban 2 days after completing nirmatrelvir/ritonavir. **C) If atrial fibrillation:** Decrease edoxaban to 30 mg daily. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	No drug interaction data available with protease inhibitors but up to a 2-fold increase in exposure is anticipated. Canadian product monograph recommends caution when using with ritonavir; 30 mg daily dose is recommended with P-glycoprotein inhibitors. ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf
◆	Elagolix (*Orilissa*)	Potential for increased elagolix concentrations and possibly decreased nirmatrelvir concentrations. Continue with usual elagolix dose during nirmatrelvir/ritonavir therapy and monitor for elagolix toxicity.	Potential for serious adverse effects, including suicidal ideation and elevation of hepatic transaminases. Elagolix AUC increased over 2-fold when coadministered with ketoconazole 400 mg daily.

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AUC = Area under the curve

June 6, 2022

Appendix (Page 6)

	Drug	Recommendation	Comments
◆	Encorafenib (*Braftovi*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing encorafenib dose as follows and monitoring for toxicity: • If taking 450 mg per day: reduce to 150 mg daily. • If taking 150 to 300 mg per day: reduce dose to 75 mg daily. Resume usual encorafenib dose 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust encorafenib should be made in conjunction with the patient's oncologist. Encorafenib AUC increased 3-fold when coadministered with posaconazole.
●	Ergot alkaloids (e.g., dihydroergotamine, ergonovine)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Potential for serious and/or life threatening adverse effects, including acute ergot toxicity.
●	Everolimus (*Certican*)	Hold everolimus and start nirmatrelvir/ritonavir 12 hours after last everolimus dose. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be guided by therapeutic drug monitoring and in conjunction with the patient's transplant provider.	Check everolimus concentrations 2 days after last dose of nirmatrelvir/ritonavir. • **If therapeutic/sub-therapeutic:** resume everolimus at 25 to 50% baseline dose. Repeat level every 2 to 4 days and adjust dose accordingly. • **If supratherapeutic:** continue to hold everolimus; repeat level in 2 to 4 days to assess resumption.
◆	Felodipine	Reduce felodipine dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.
●	Flurazepam	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
◆	Fostamatinib (*Tavalisse*)	Monitor for toxicity including diarrhea, hypertension, hepatotoxicity, and neutropenia. If significant toxicity occurs, consider interruption of fostamatinib with reintroduction 2 days after completing nirmatrelvir/ritonavir.	Fostamatinib active metabolite AUC increased 102% when coadministered with ketoconazole.
●	Glecaprevir/ Pibrentasvir (*Maviret*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Glecaprevir exposure is increased over 4-fold with ritonavir and is associated with increased risk of alanine aminotransferase (ALT) elevation. In patients who are planning to start Hepatitis C (HCV) treatment, glecaprevir/pibrentasvir treatment should be deferred.
◆	Hydrocodone	Reduce dose by about 50% or switch to equivalent dose of hydromorphone: • Multiply hydrocodone dose by 0.25 to get equivalent hydromorphone dose. • Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance. Monitor for signs of opioid toxicity. Resume usual hydrocodone dose 2 days after completing nirmatrelvir/ritonavir.	Hydrocodone is metabolized to active metabolites: hydromorphone and norhydrocodone. Hydrocodone AUC increased by 90% when coadministered with ritonavir/ombitasvir/ paritaprevir combination.

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AUC = Area under the curve

June 6, 2022

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	Drug	Recommendation	Comments
●	Ibrutinib (*Imbruvica*)	Consider alternate COVID-19 therapy. Alternatively, consider holding ibrutinib and starting nirmatrelvir/ritonavir 12 hours after the last ibrutinib dose. Restart ibrutinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust ibrutinib should be made in conjunction with the patient's oncologist. **It may be dangerous to interrupt therapy in patients with high volume chronic lymphocytic leukemia or mantle cell lymphoma due to disease flare and/or cytokine release.** Ibrutinib AUC increased 26-fold when coadministered with ketoconazole.
●	Lomitapide (*Juxtapid*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Lomitapide AUC increased 27-fold when coadministered with ketoconazole.
●	Lovastatin	Stop lovastatin at least 12 hours before starting nirmatrelvir/ritonavir. Restart 5 days after completing nirmatrelvir/ritonavir.	Contraindicated due to potential for severe toxicity including rhabdomyolysis and elevated liver function tests.
●	Meperidine (*Demerol*)	Do not coadminister. Switch meperidine to an equivalent dose of hydromorphone: • Multiply meperidine dose by 0.02 to get equivalent hydromorphone dose. • Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance. Monitor for signs of opioid toxicity. Resume usual meperidine dose 2 days after completing nirmatrelvir/ritonavir.	Normeperidine AUC increased 50% when coadministered with ritonavir. Higher levels of normeperidine can cause central nervous system excitation and seizures.
●	Midazolam, oral	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Coadministration may result in large increases in oral midazolam concentrations with the potential for serious events such as prolonged or increased sedation or respiratory depression.
◆	Modafinil	No dose adjustment required. Monitor for anxiety and agitation.	Coadministration could potentially increase modafinil exposure due to CYP3A4 inhibition. Modafinil is a moderate inducer of CYP3A4, but a clinically significant effect on nirmetrelvir/ritonavir exposure is unlikely.
●	Neratinib (*Nerlynx*)	Hold and start nirmatrelvir/ritonavir 24 hours after the last neratinib dose. Restart neratinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Neratinib AUC increased almost 5-fold when coadministered with ketoconazole.
◆	Nifedipine	Reduce nifedipine dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.
◆	Nilotinib (*Tasigna*)	**Chronic phase chronic myelogenous leukemia (CML):** Hold nilotinib if possible, restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider dose reduction to 400 mg PO daily and monitor for toxicity. **Accelerated or blast phase CML:** Do not coadminister. Consider an alternate COVID-19 therapy.	Decisions to hold or dose-adjust nilotinib should be made in conjunction with the patient's oncologist. Canadian monograph recommends holding if using CYP3A4 inhibitors, or monitoring for QTc if treatment interruption is not possible. A 50% dose reduction is recommended based on expected effect on nilotinib exposures. Deeken JF, Pantanowitz I, Dezube BJ. Targeted therapies to treat non-AIDS-defining cancers in patients with HIV on HAART therapy: treatment considerations. *Curr Opin Oncol* 2009; 21(5): 445-54. doi: 10.1097/CC.0b013e32832f3e04 Nilotinib AUC increased 3-fold when coadministered with ketoconazole.

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AUC = Area under the curve

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	Drug	Recommendation	Comments
●	Nitrazepam (*Mogadon*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
◆	Oxycodone (*Percocet, OxyNEO*)	Reduce dose of oxycodone by 66% or switch to equivalent dose of hydromorphone: • Multiply oxycodone dose by 0.3 to get equivalent hydromorphone dose. • Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance. Monitor for signs of opioid toxicity. Resume usual oxycodone dose 2 days after completing nirmatrelvir/ritonavir.	Oxycodone half-life increased 2-fold and AUC increased between 3 and 4-fold when coadministered with other potent 3A4 inhibitors (i.e., voriconazole).
◆	Quetiapine (*Seroquel*)	Reduce to one-sixth of original dose and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, dizziness, and sedation.	Quetiapine AUC increased 5 to 8-fold when coadministered with ketoconazole.
●	Quinine	**For treatment of leg cramps:** Hold and restart 2 days after completing nirmatrelvir/ritonavir. **For treatment of malaria:** Use an alternative COVID-19 agent.	Quinine AUC increased 4-fold and conversion to active metabolite was markedly inhibited when coadministered with ritonavir 200 mg twice daily.
◆	Rifabutin	Reduce rifabutin to 150 mg once daily; return to 300 mg once daily 2 days after completing nirmatrelvir/ritonavir.	Canadian monograph recommends 150 mg three times a week, but the dose been found to be too low and contributes to resistance. The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents recommends using rifabutin 150 mg daily when used with a ritonavir-boosted protease inhibitor. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/drug-interactions-between-protease-inhibitors-and-other-drugs?view=full Significant increases in exposures of rifabutin (>3-fold) and metabolite (>40-fold) observed when coadministered with lopinavir/ritonavir 400/100 mg twice daily.
◆	Risperidone (*Risperdal*), oral	Reduce risperidone dose by 25 to 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, extrapyramidal symptoms, and sedation.	Risperidone AUC increased up to 2-fold when coadministered with ketoconazole. Avoid coadministration in patients stabilized on risperidone long-acting injection.
●	Rivaroxaban (*Xarelto*)	*Next page*	*Next page*

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AUC = Area under the curve

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	Drug	Recommendation	Comments
●	Rivaroxaban (*Xarelto*)	If possible, use alternative COVID-19 agent. If not possible, then: **A) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold rivaroxaban. 24 hours after the last dose of rivaroxaban, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmaltrevir/ritonavir. Restart rivaroxaban 2 days after completing nirmatrelvir/ritonavir. ⚠ *High risk of clot:* Hold rivaroxaban. 24 hours after the last dose of rivaroxaban, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours if >90 kg; ◦ **Enoxaparin** 1 mg/kg every 12 hours (preferred) OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart rivaroxaban 2 days after completing nirmatrelvir/ritonavir. **B) If atrial fibrillation:** Hold rivaroxaban. 24 hours after the last dose of rivaroxaban, start nirmatrelvir/ritonavir AND edoxaban 30 mg daily. Finish edoxaban 1 day after completing nirmatrelvir/ritonavir. Restart rivaroxaban 2 days after completing nirmatrelvir/ritonavir.	Rivaroxaban AUC and Cmax increased by 153% and 55%, respectively, when coadministered with ritonavir 600 mg twice daily in healthy volunteers. Observational data from Italy found a 600 to 3000% increase in rivaroxaban levels in combination with *antivirals* containing ritonavir in hospitalized patients. Testa S, Prandoni P, Paoletti O et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. *J Thromb Haemost.* 2020;18:1320–1323. https://doi.org/10.1111/jth.14871 ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf
◆	Rosuvastatin	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce to 10 mg daily. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Rosuvastatin AUC increased 2-fold and Cmax increased almost 5-fold when coadministered with lopinavir/ritonavir 400/100 mg twice daily.
●	Salmeterol (*Serevent, Advair*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Potential for serious and/or life-threatening adverse effects, including cardiac arrhythmias (prolonged QTc).
◆	Sildenafil for erectile dysfunction (*Viagra*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce dose to 25 mg once every 48 hours. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Sildenafil AUC increased 2 to 11-fold when coadministered with protease inhibitors.
●	Silodosin (*Rapaflo*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Silodosin AUC increased over 3-fold when coadministered with ketoconazole.
●	Simvastatin	Stop simvastatin at least 12 hours before starting nirmatrelvir/ritonavir. Restart 5 days after completing nirmatrelvir/ritonavir.	Contraindicated due to potential for severe toxicity including rhabdomyolysis and elevated liver function tests.
●	Sirolimus (*Rapamune*)	Hold sirolimus and start nirmatrelvir/ritonavir 24 to 48 hours after the last sirolimus dose. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be done in conjunction with the patient's transplant provider. Use therapeutic drug monitoring to guide sirolimus dose re-adjustment after completion of nirmatrelvir/ritonavir.	Check sirolimus concentration 2 days after last dose of nirmatrelvir/ritonavir. • **If therapeutic/subtherapeutic:** resume sirolimus at 50% of baseline dose. Repeat level every 7 days and dose-adjust accordingly. • **If supratherapeutic:** continue to hold sirolimus and repeat level in 5 to 7 days to assess resumption.

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Cmax = Maximum (or peak) serum concentration
AUC = Area under the curve

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	Drug	Recommendation	Comments
●	Tacrolimus (*Prograf, Advagraf, Envarsus*)	Immediate release (*Prograf*, generics): hold tacrolimus and start nirmatrelvir/ritonavir 12 hours after the last tacrolimus dose. Extended (*Advagraf*) or prolonged (*Envarsus*) release: hold the long acting tacrolimus and start nirmatrelvir/ritonavir 24 hours after the last tacrolimus dose. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be guided by therapeutic drug monitoring and in conjunction with the patient's transplant provider.	For all forms of tacrolimus: check tacrolimus concentrations 2 days after the last dose of nirmatrelvir/ritonavir. • **If therapeutic/subtherapeutic:** resume tacrolimus at 25 to 75% of baseline dose; repeat level every 2 to 4 days and adjust dose accordingly. • **If supratherapeutic:** continue to hold tacrolimus; repeat level in 2 to 4 days to assess resumption.
◆	Tadalafil for erectile dysfunction (*Cialis*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce the dose to 10 mg once every 72 hours. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Tadalafil AUC increased 124% when coadministered with ritonavir 200 mg twice daily.
●	Tamsulosin (*Flomax*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, may consider using 0.4 mg daily or giving every other day in patients with heightened risk of urinary retention. Monitor for hypotension.	Tamsulosin AUC increased almost 3-fold when coadministered with ketoconazole.
●	Ticagrelor (*Brilinta*)	**Acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI):** • **If <1 month since ACS:** Suggest alternative COVID-19 agent. • **If <3 months since ACS or <1 month since PCI (no ACS):** Switch to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) during nirmatrelvir/ritonavir therapy. • **If >3 months since ACS or >1 month since PCI (no ACS):** Consider temporarily holding ticagrelor (i.e., no switching) during nirmatrelvir/ritonavir therapy and resuming after. If not taking acetylsalicylic acid (ASA), consider switching to prasugrel (if age <70, weight >60 kg, and no history of stroke/TIA) or half-dose of ticagrelor (45 mg twice daily).	Ticagrelor AUC increased 36% when coadministered with a single dose of ritonavir 100 mg.
◆	Tramadol	Reduce tramadol dose by 50% and monitor for pain relief and opioid toxicity. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Inhibition of CYP3A4 may increase tramadol concentrations. Inhibition of CYP2D6 can decrease conversion of tramadol to a more active metabolite, but this is not expected to be significant when coadministered with nirmatrelvir/ritonavir.
●	Triazolam (*Halcion*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended. Triazolam half-life increased from 4 to 50 hours when coadministered with ritonavir 200 mg x 4 doses.
●	Vardenafil (*Levitra*) for erectile dysfunction	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Vardenafil AUC increased 49-fold when coadministered with ritonavir 600 mg twice daily.
◆	Verapamil	Reduce verapamil dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.

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TIA = Transient ischemic attack
AUC = Area under the curve

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Drug	Recommendation	Comments
Vinblastine	Vinblastine may be held in the context of acute infection. Restart vinblastine at least 2 days after completing nirmatrelvir/ritonavir. Alternatively, vinblastine may be coadministered with close monitoring for hematologic and neurotoxicity. Some providers may wish to empirically reduce vinblastine dose, especially in patients who have previously experienced or are at high risk for toxicity.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Vinblastine AUC increased almost 2-fold when coadministered with ritonavir. Increased risk of autonomic and peripheral neurotoxicity and neutropenia have been reported with coadministration of ritonavir and vinblastine.
Vincristine	Vincristine may be held in the context of acute infection. Restart vincristine 2 days after completing nirmatrelvir/ritonavir. Alternatively, vincristine may be coadministered with close monitoring for hematologic and neurotoxicity. Some providers may wish to empirically reduce vincristine dose, especially in patients who have previously experienced or are at high risk for toxicity.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Increased rates of hematologic toxicity and neuropathy (including autonomic neuropathy) have been reported with coadministration of ritonavir and vincristine.
Warfarin	Monitor for signs of increased bleeding and bruising. Check international normalized ratio (INR) if clinically indicated.	Potential for increased warfarin concentrations when coadministered with nirmatrelvir/ritonavir.
Ziprasidone (*Zeldox*)	No dose adjustment required. Monitor for dizziness, extrapyramidal symptoms, and sedation.	Only one-third of ziprasidone dose is metabolized by CYP450. Ziprasidone AUC increased 35 to 40% when coadministered with ketoconazole.
Zolpidem (*Sublinox, Ambien*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If coadministration required, reduce zolpidem dose by 50%.	Zolpidem AUC increased 70% when coadministered with ketoconazole.
Zopiclone (*Imovane*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If coadministration required, reduce zopiclone dose by 50%.	Potential for increased zopiclone exposures when coadministered with nirmatrelvir/ritonavir.

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AUC = Area under the curve