NORTH METROPOLITAN HEALTH SERVICE

NMHS Therapeutic Guidelines for current COVID-19 Treatments (version 14M22)

A guide for currently recommended pharmacotherapies for management of COVID-19

Note: these recommendations serve as a guide only and clinical judgement should take precedence for each individual case.

Key Terms									
NS	Sodium chloride 0.9% (normal saline)	SAS	Special Access Scheme	OAT	Organic anion transporter	MATE	Multi-drug and toxic extrusion protein	OATP	Organic anion transporting polypeptide
G5%	Glucose 5% (dextrose 5%)	mg	Milligrams	OCT	Organic cationic transporter	ATSI	Aboriginal and Torres Strait Islander		
WFI	Water for Injections	mcg	Micrograms	BRCP	Breast cancer resistance protein	NIV	Non-invasive Ventilation		

DISEASE SEVERITY	ESTABLISHED DEFINITION	OXYGEN REQUIREMENTS	THERAPEUTIC OPTIONS

Mild illness
Confirmed COVID-19 infection without evidence of viral pneumonia or hypoxia
	No clinical features suggestive of moderate or more severe disease
	• No or mild symptoms and signs (fever, cough, sore throat, headache, myalgia, loss of taste/smell)
	• No new shortness of breath or difficult breathing on exertion
	• No evidence of lower respiratory tract disease during clinical assessment or on imaging
		Not requiring oxygen	**REFER TO WA HEALTH COVID-19 TREATMENT DECISION TREE FOR GUIDANCE WITH TREATMENT SELECTION (Appendix 1)**
			• **Budesonide (inhaled)**
			  • For non-hospitalised patients within 14 days of symptom onset and at risk of disease progression
			• **Nirmatrelvir + Ritonavir (Paxlovid®)**
			  • Not fully vaccinated individuals within 5 days of symptom onset with ≥1 risk factors for progression
			  • Immunosuppressed individuals within 5 days of symptom onset regardless of vaccination status
			• **Sotrovimab** (refer to **Appendix 1A**)
			  • Not fully vaccinated individuals within 5 days of symptom onset with ≥1 risk factors for progression
			  • Immunosuppressed, Pregnancy (especially if unvaccinated or immunosuppressed)
			  • ATSI > 35 yo with high risk co-morbidities
			• **Molnupiravir (Lagevrio®)**
			  • Not fully vaccinated individuals within 5 days of symptom onset with ≥1 risk factors for progression
			  • Immunosuppressed individuals within 5 days of symptom onset regardless of vaccination status
			• **Casirivimab plus Imdevimab (Ronapreve®)** **Subject to availability**
			  • Alternative to sotrovimab for patients who are not infected with Omicron variant

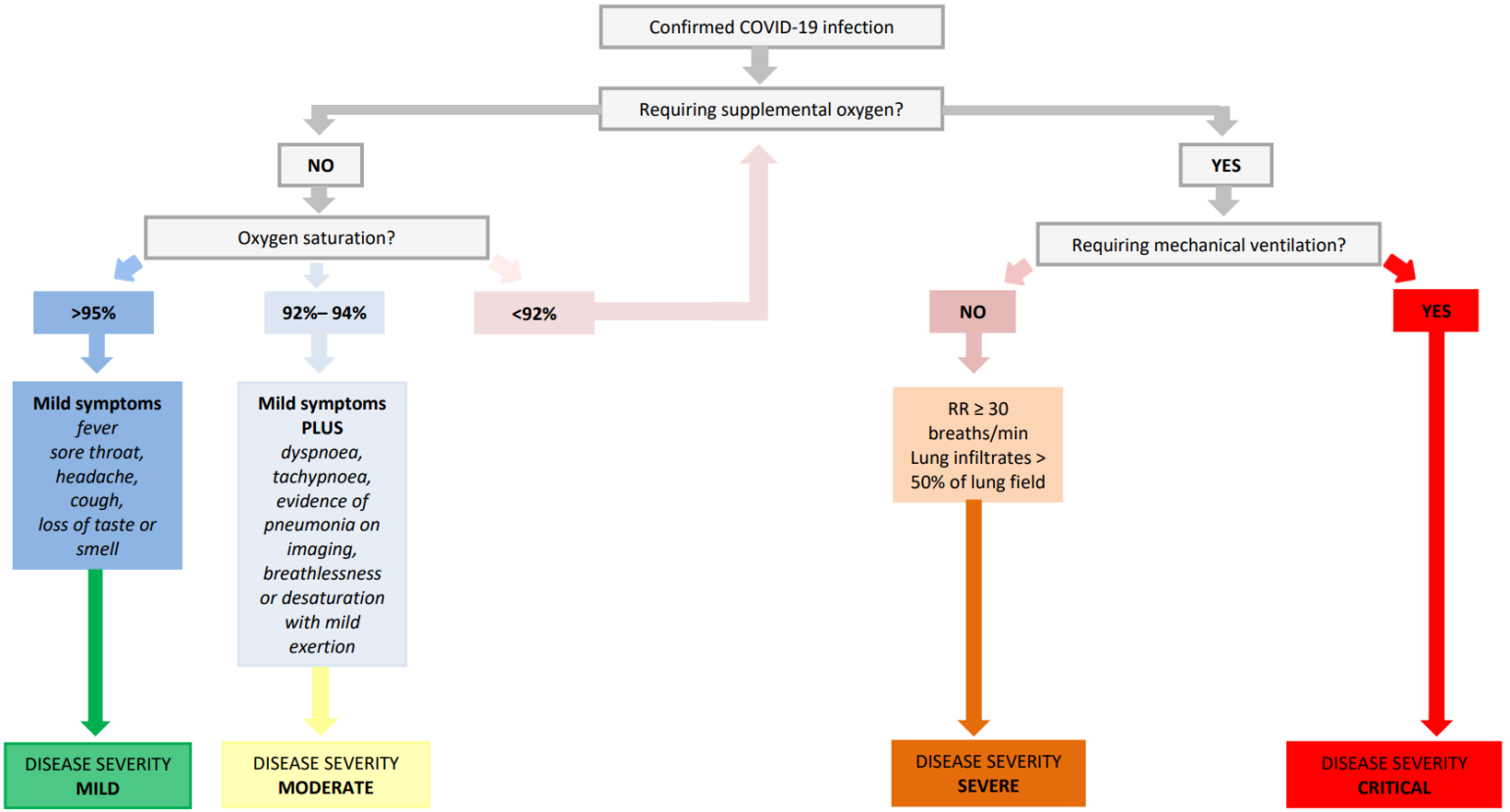
Moderate illness *Confirmed COVID-19 infection with clinical signs of pneumonia (fever, dyspnoea, ↑ RR) but not requiring oxygen*	A stable patient with evidence of lower respiratory tract disease during clinical assessment including • Oxygen saturation 92-94% on room air at rest • Desaturation or breathlessness with mild exertion OR evidence on imaging	Not requiring oxygen	Same therapeutic options as for **Mild illness**
Severe illness *Confirmed COVID-19 infection with clinical signs of pneumonia AND requiring oxygen but NOT ventilation*	A patient with signs of moderate disease who is deteriorating OR A patient who meets any of the criteria below • Respiratory rate ≥ 30 breaths/min • Oxygen saturation ≤ 92% on room air at rest or requiring oxygen • Lung infiltrates > 50% of lung field	Requiring oxygen but NOT ventilation	• **Corticosteroids (eg dexamethasone)** • For all patients requiring oxygen (If pregnant, use prednisolone or hydrocortisone) • **Remdesivir** If features of systemic inflammation*, or progression despite steroids +/- remdesivir consider: • **Baricitinib** (1st line, <u>unless pregnant</u>) • **Tocilizumab** (2nd line – reserved for pregnant patients, eGFR< 15mls/min)

Critical illness
Confirmed COVID-19 infection requiring ventilation
	A patient meeting any of the criteria below
	• Respiratory failure
	  • Severe respiratory failure (PaO_2/FiO_2 < 200)
	  • Respiratory distress or acute respiratory distress syndrome (ARDS)
	  • Deteriorating despite non-invasive forms of respiratory support
	  • Requiring mechanical ventilation
	• Hypotension or shock
	• Impairment of consciousness
	• Other organ failure
		Requiring ventilation	• **Corticosteroids** (eg dexamethasone)
			  • For all patients requiring oxygen (If pregnant, use prednisolone or hydrocortisone)
			If features of systemic inflammation*, consider:
			• **Baricitinib** (1st line, <u>unless pregnant</u>)
			• **Tocilizumab** (2nd line – reserved for pregnant patients, eGFR< 15mls/min)

*systemic inflammation defined as

For baricitinib – elevated levels of CRP, ferritin, LDH or D-dimer For tocilizumab – CRP > 75

Simplified flow chart aid to assist with determining the severity of COVID-19 infection (mild, moderate, severe, critical).
NB. with each individual case these guidance algorithms serve mainly as a guide and clinical judgment with specialist expertise should be acknowledged and considered.



COVID-19 PHARMACOTHERAPEUTIC GUIDE (CURRENTLY AVAILABLE THERAPIES)

MEDICATION	WHEN TO USE OR COMMENCE	USE IN RELATION TO OXYGEN REQUIREMENTS				DOSAGE	DOSAGE ADJUSTMENTS	CONTRA-INDICATIONS / PRECAUTIONS	PREGNANCY/ BREASTFEEDING	POTENTIAL DRUG INTERACTIONS (see relevant appendices for details)	ACCESS/ APPROVAL
		Not on oxygen	SUPPLEMENTAL	VENTILATED							
			Low/High flow oxygen	NIV	Invasive mechanical ventilation						
ANTIVIRAL AGENTS											
REMDESIVIR	**SEVERE ILLNESS** Consider in patients with severe illness who require supplemental oxygen but NOT invasive or non-invasive ventilation (within first 7 days of symptom onset)	Do not use	Start therapy	Continue if already receiving Do not initiate	Continue if already receiving Do not initiate	Currently a 5-day course is recommended **Day 1** = 200mg **Days 2-5** = 100mg daily	**RENAL** CrCl < 30ml/min • Caution with use due to accumulation of cyclodextrin **HEPATIC** • No data	Hypersensitivity to any of the excipients Eg sulfobutyl betadex sodium CrCl < 30ml/min ALT/AST ≥ 5 x ULN NIV or Invasive Ventilation	Pregnancy • Category B2 • Considered safe to use Breastfeeding • Limited data *Remdesivir has poor oral bioavailability so unlikely to receive clinically relevant levels from breastmilk*	Avoid concomitant use with chloroquine/ hydroxychloroquine Substrate for • CYP2C8 / 2D6 / 3A4 • OATP1B1 • P-gp Inhibitor of • CYP3A4 • OATP1B1 / 1B3 Inducer of • CYP1A2 / 3A4	ID Consultant approval and REDCap form completion. Only available through National Medical Stockpile
SOTROVIMAB	**MILD ILLNESS** **MODERATE ILLNESS** Consider in not fully vaccinated patients with mild or moderate illness who are not requiring supplemental oxygen and have ≥ 1 risk factors for disease progression, within 5 days of symptom onset. Also consider in immunocompromised patients, pregnancy (2nd or 3rd trimester, esp if unvaccinated or immunocompromised) or ATSI > 35yo with co-morbidities **Refer to Appendix 1 and 1A**	Consider starting if meets inclusion criteria	Do not use	Do not use	Do not use	A **single** 500mg IV dose	No dosage adjustments required for organ impairment • Metabolised by tissue proteolytic enzymes	Hypersensitivity to any of the excipients First trimester of pregnancy Known reaction to prior monoclonal antibodies	Pregnancy • Category B2 • Considered safe to use in second and third trimester Breastfeeding • Limited data *Sotrovimab has a high MW and unlikely to enter the breast milk in appreciable amounts*	Unlikely to involve interactions with cytochromeP450 enzymes , P-gp or other transporter systems	ID Consultant approval and REDCap form completion. Only available through National Medical Stockpile
CASIRIVIMAB plus IMDEVIMAB **SUBJECT TO AVAILABILITY**	**MILD ILLNESS** **MODERATE ILLNESS** An alternative to sotrovimab therapy in patients infected with non-Omicron variant only	Consider starting as an alternative to sotrovimab for non-Omicron cases only	Do not use	Do not use	Do not use	1200mg (600mg of casirivimab + 600mg of imdevimab) as a **single** IV dose Subcutaneous route is an option when used as prophylaxis For treatment – use IV route	No dosage adjustments required for organ impairment • Metabolised by tissue proteolytic enzymes	Infection with Omicron variant Hypersensitivity to any of the excipients, including monoclonal antibodies First trimester of pregnancy	Pregnancy • Category B2 • Considered safe to use Breastfeeding • Limited data *Limited amounts expected to enter breast milk*	Unlikely to involve interactions with cytochromeP450 enzymes , P-gp or other transporter systems	Not currently available

MEDICATION	WHEN TO USE OR COMMENCE	USE IN RELATION TO OXYGEN REQUIREMENTS				DOSAGE	DOSAGE ADJUSTMENTS	CONTRA-INDICATIONS / PRECAUTIONS	PREGNANCY/ BREASTFEEDING	POTENTIAL DRUG INTERACTIONS (see relevant appendices for details)	ACCESS/ APPROVAL
		Not on oxygen	SUPPLEMENTAL	VENTILATED							
			Low/High flow oxygen	NIV	Invasive mechanical ventilation						
NIRMATRELVIR plus RITONAVIR (PAXLOVID®)	**MILD ILLNESS** **MODERATE ILLNESS** Consider use in not fully vaccinated patients with mild to moderate illness who are not requiring supplemental oxygen and have ≥ 1 risk factors for disease progression, within 5 days of symptom onset. Also consider in immunocompromised patients with mild to moderate illness regardless of vaccination status **Refer to Appendix 1 and 1A**	Consider starting if meets inclusion criteria	Do not use	Do not use	Do not use	**300mg Nirmatrelvir** (two 150mg tabs) PLUS **100mg Ritonavir** (one 100mg tab) taken together orally **every 12 hours** for **FIVE days**	**RENAL** CrCl (ml/min) ≥ 30 to < 60 : 150mg Nirmatrelvir PLUS 100mg Ritonavir every 12 hours for FIVE days < 30 – AVOID **HEPATIC** Mild to moderate (Child Pugh A or B) No dosage adjustment Severe (Child Pugh C) – AVOID	Hypersensitivity to either active ingredient Avoid in severe renal impairment (<30ml/min) or severe hepatic impairment Avoid in combination with drugs that are highly dependent on CYP3A for clearance or drugs that are potent inducers of CYP3A	Pregnancy • Category B3 **Not recommended** No human data relating to safety of nirmatrelvir during pregnancy Breastfeeding No data available on presence of nirmatrelvir in human or animal milk or its effects on infant	Nirmatrelvir and ritonavir are CYP3A inhibitors and substrates Nirmatrelvir is a likely inhibitor of • P-gp • MATW1 • OATP1B1 Ritonavir also an inhibitor of • CYP2D6, 2C9, 2C19, 2A6, 1A2, 2E1 • P-gp Inducer of • CYP1A2, 2C8, 2C9, 2C19	ID Consultant approval and REDCap form completion. Only available through National Medical Stockpile
MOLNUPIRAVIR	**MILD ILLNESS** **MODERATE ILLNESS** Consider use in not fully vaccinated patients with mild to moderate illness who are not requiring supplemental oxygen and have ≥ 1 risk factors for disease progression, within 5 days of symptom onset. Also consider in immunocompromised patients with mild to moderate illness regardless of vaccination status **Refer to Appendix 1 and 1A**	Consider starting if meets inclusion criteria	Do not use	Do not use	Do not use	**800mg Molnupiravir** (four 200mg capsules) taken orally **every 12 hours** for **FIVE days**	**RENAL** It is not expected that any dosage adjustment is required for any degree of renal impairment **HEPATIC** It is not expected that any dosage adjustment is required for any degree of hepatic impairment	Hypersensitivity to molnupiravir or any of the excipients	Pregnancy • Category D AVOID USE Based on animal data, molnupiravir may cause foetal harm. Women of childbearing potential should use effective contraception for duration of treatment and for at least 4 days after final dose Men who are sexually active with women of childbearing potential should use effective contraception during and for 3 months after treatment	No clinically relevant drug interactions have been identified from limited data available Molnupiravir (or its active component) have not demonstrated any influence on CYP enzymes or other drug transporters	To access **PBS stock** -Streamlined Authority prescription required – stock available from select community pharmacies To access **NMS stock** -ID Consultant approval and REDCap form completion

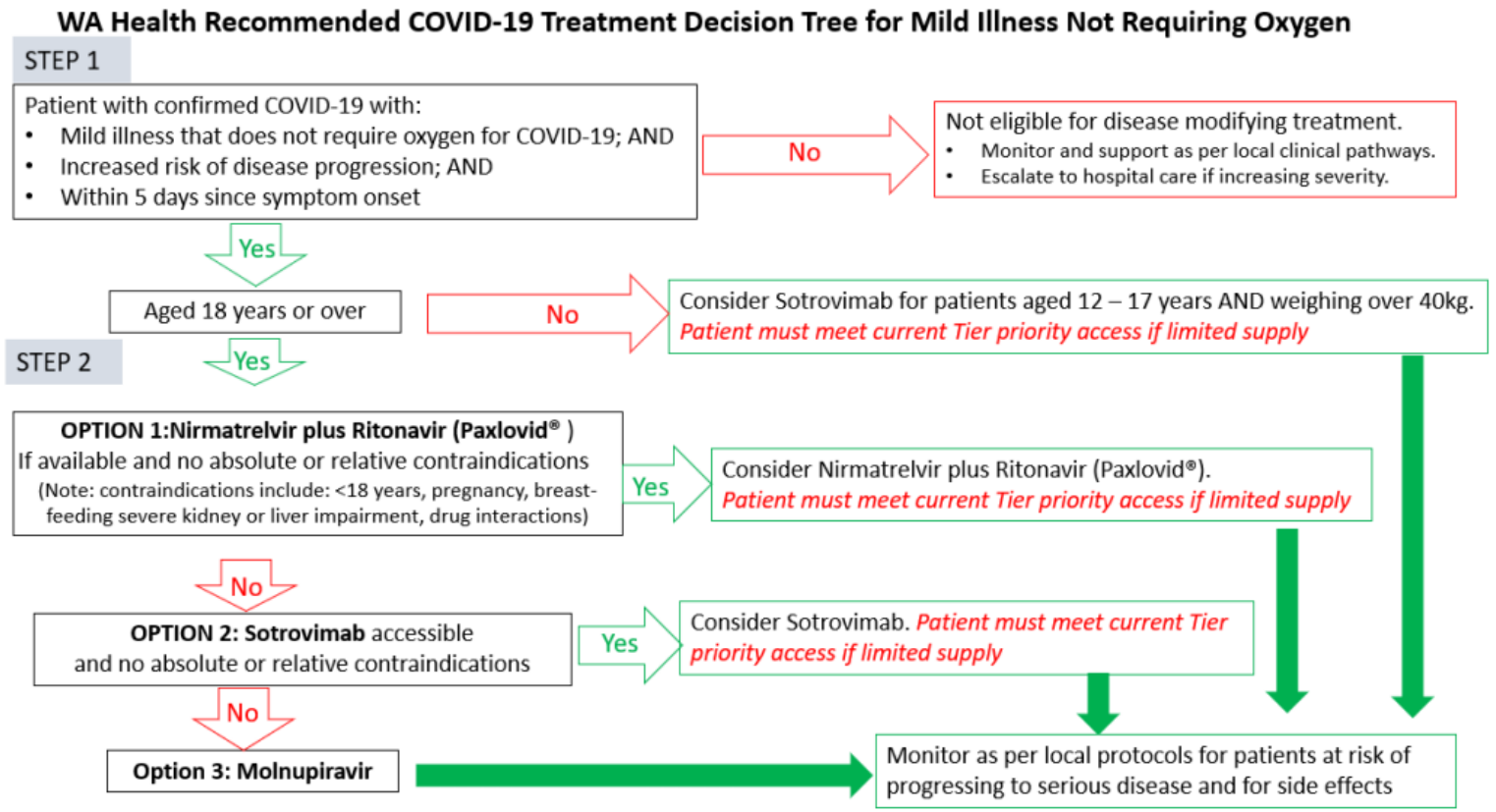
									Lactation It is unknown if molnupiravir is present in human milk. Potential for adverse effects in the infant so avoid breastfeeding during treatment and for 4 days after final dose		
IMMUNOMODULATING AGENTS											
MEDICATION	**WHEN TO USE OR COMMENCE**	**USE IN RELATION TO OXYGEN REQUIREMENTS**				**DOSAGE**	**DOSAGE ADJUSTMENTS**	**CONTRA-INDICATIONS / PRECAUTIONS**	**PREGNANCY/ BREASTFEEDING**	**POTENTIAL DRUG INTERACTIONS** (see relevant appendices for details)	**ACCESS/ APPROVAL**
		Not on oxygen	**SUPPLEMENTAL**	**VENTILATED**							
			Low/High flow oxygen	**NIV**	**Invasive mechanical ventilation**						
CORTICOSTEROIDS Eg dexamethasone, hydrocortisone, prednisolone	**SEVERE ILLNESS** **CRITICAL ILLNESS** Use in all patients with severe or critical illness who are either requiring supplemental oxygen or ventilation	Do not use	Start therapy	Start therapy or continue if already receiving	Start therapy or continue if already receiving	Dexamethasone 6mg daily (IV / oral) for up to 10 days If pregnant, the preferred options (as placental transfer is limited) are <u>Hydrocortisone</u> 50mg IV every 6 hours for up to 10 days <u>Prednisolone</u> 50mg oral daily for up to 10 days **If at risk of preterm birth**; if foetal lung maturation is indicated then Betamethasone is preferred (dexamethasone is a suitable alternative)	No dosage adjustments required for renal or hepatic impairment	Hypersensitivity to dexamethasone	Pregnancy • Category C Preferred options are hydrocortisone or prednisolone Breastfeeding • Limited data Alternative options available (Prednisolone, Hydrocortisone)	Dexamethasone is a substrate for CYP3A4 Theoretical interaction with CYP3A4 inducers • May increase metabolism to ↓ dexamethasone levels CYP3A4 inhibitors • May decrease metabolism to ↑ dexamethasone levels	Unrestricted

MEDICATION	WHEN TO USE OR COMMENCE	USE IN RELATION TO OXYGEN REQUIREMENTS				DOSAGE	DOSAGE ADJUSTMENTS	CONTRA-INDICATIONS / PRECAUTIONS	PREGNANCY/ BREASTFEEDING	POTENTIAL DRUG INTERACTIONS (see relevant appendices for details)	ACCESS/ APPROVAL
		Not on oxygen	SUPPLEMENTAL	VENTILATED							
			Low/High flow oxygen	NIV	Invasive mechanical ventilation						
BUDESONIDE (INHALED)	**MILD ILLNESS** **MODERATE ILLNESS** Use in patients with mild to moderate illness within 14 days of symptom onset who do not require supplemental oxygen and are at risk for disease progression	Start if meets inclusion criteria	Do not use	Do not use	Do not use	Use breath-actuated inhaler (eg Symbicort®, Pulmicort®) 800microg twice a day for up to 14 days	No dosage adjustments required	Hypersensitivity to budesonide	Pregnancy • Category A • Safe to use Breastfeeding • Safe to use	Nil regarded as significant given the minimal systemic absorption following inhaled administration	Unrestricted
BARICITINIB	**SEVERE ILLNESS** **CRITICAL ILLNESS** Consider use in patients with severe or critical illness who are either requiring supplemental oxygen or ventilation and showing signs of systemic inflammation. (CRP>75, Ferritin >500, D-dimer >0.5) Perform latent infection screen but do not delay commencement (Eg Hep B, Hep C, HIV serology-consider TB QuantiFERON® and Strongyloides serology based on risk)	Do not use	Consider starting therapy	Consider starting therapy or continue if already receiving	Consider starting therapy or continue if already receiving	4mg daily orally for up to 14 days Always use in combination with corticosteroids	**RENAL** CrCl 30-60ml/min • 2mg daily CrCl 15-30ml/min • 1mg daily Not recommended if CrCl <15ml/min or requiring RRT **HEPATIC** No dosage adjustment in mild to moderate hepatic impairment Avoid in severe hepatic impairment	**Avoid in pregnancy or lactation** Avoid combining with other immune-modulating agents (except corticosteroids) Avoid if cytopaenic: Neut< 1.0 Lymph <0.2 Hb <80	Pregnancy • Avoid use • **Category D** Breastfeeding • Limited data *Not recommended during treatment and for at least 3 days after the last dose*	In vitro, baricitinib is a substrate for • CYP3A4 • OAT3 • P-gp • BCRP • MATE2-K Baricitinib exhibits negligible effect on cytochrome P450 enzymes , P-gp, OAT, BCRP or MATE Caution when combining with other • Immunosuppressants • Immunomodulators • Clozapine • Live vaccines	Consultant approval to commence Retrospective Streamlined IPA required

MEDICATION	WHEN TO USE OR COMMENCE	USE IN RELATION TO OXYGEN REQUIREMENTS				DOSAGE	DOSAGE ADJUSTMENTS	CONTRA-INDICATIONS / PRECAUTIONS	PREGNANCY/ BREASTFEEDING	POTENTIAL DRUG INTERACTIONS (see relevant appendices for details)	ACCESS/ APPROVAL
		Not on oxygen	SUPPLEMENTAL	VENTILATED							
			Low/High flow oxygen	NIV	Invasive mechanical ventilation						
TOCILIZUMAB	**SEVERE ILLNESS** **CRITICAL ILLNESS** Consider use in patients with severe or critical illness who are either requiring supplemental oxygen or ventilation and showing signs of systemic inflammation (CRP>75, Ferritin >500, D-dimer >0.5)	Do not use	Consider starting therapy #	Consider starting therapy# or continue if already receiving	Consider starting therapy# or continue if already receiving	Dosage is weight based (use actual body weight) as a single IV dose >90kg: 800mg 66-90kg: 600mg 41-65kg: 400mg ≤40kg: 8mg/kg Doses are capped	No dosage adjustments for renal or hepatic impairment or age have been established	Hypersensitivity to any component of the product Known reaction to prior monoclonal antibodies Hypersensitivity to Chinese hamster ovary	Pregnancy • Category C • Preferred agent over baricitinib Breastfeeding • Limited data • Preferred agent over baricitinib	Tocilizumab has no inhibitory or inducing effects on cytochrome P450 enzymes No clinically relevant pharmacological interactions have been noted Caution when	Consultant approval to commence Retrospective Streamlined IPA required

	# Generally reserved for use as an alternative in patients where baricitinib is not clinically suitable Perform latent infection screen but do not delay commencement (Eg Hep B, Hep C, HIV serology- consider TB QuantiFERON® and Strongyloides serology based on risk)					at 800mg (max) A request for a second dose 12-24 hours after the first dose may be considered, taking into account patient status and stock availability		cell products Use with caution in patients who are neutropenic, thrombo-cytopaenic or immuno-suppressed	*Poor oral bioavailability secondary to inactivation within GI tract*	combining with other • Immunosuppressants • Immunomodulators • Clozapine • Live vaccines	

APPENDIX 1 (adapted from the *WA Health Prioritisation of COVID-19 Medications document*, Version 1 3/3/22)



To initiate any of the treatments within this treatment flow chart every patient must meet **ALL** of the following criteria to be considered eligible for the indicated treatment option

1. Patient is confirmed COVID-19 positive AND
2. Is symptomatic (must be within 5 days of initial symptom onset and not requiring supplemental oxygen (in relation to COVID-19 infection) AND
3. Patient weight is ≥ 40kg AND
4. Patient age is ≥ 12 years of age AND
5. Meets the criteria for access to COVID-19 therapies (refer to **Appendix 1A**)

APPENDIX 1A

Due to uncertainty regarding stock availability with emerging COVID-19 pharmacological therapies such as Sotrovimab and the oral antiviral agents, prioritisation for access to these medications has been devised into 3 categories based on eligibility criteria established by specialist working groups, with reference to the COMET-ICE trial results.
To ensure equity of access to all relevant groups and preservation of the limited stock for patients at highest risk of disease progression, allocation of Sotrovimab and the oral antiviral agents will be prioritised based on this eligibility criteria/assessment tool and individual patient factors (eg pregnancy) and subsequent release of stock will follow a staged process (which will be dictated by stock availability and supply)

COVID-19 THERAPY AVAILABILITY STAGE	ACCESSIBILITY
STAGE 1	Limited supply available; access only granted to TIER 1 risk categories
STAGE 2	Steady supply available; access granted to TIER 1 and TIER 2 risk categories
STAGE 3	Unrestricted supply available; access granted to TIER 1, TIER 2 and TIER 3 risk categories

COVID-19 THERAPY PRIORITY ASSESSMENT TOOL TIER system based on National Institutes of Health Statement on Patient Prioritisation for Outpatient Therapies		
TIER	**AT RISK GROUP**	**ELIGIBILITY / CRITERIA**
TIER 1	**UNVACCINATED AND AT VERY HIGH RISK FOR SEVERE DISEASE**	**Unvaccinated** AND **age greater than 75 years** OR **Unvaccinated** AND **age greater than 65 years** WITH at least one other **recognised clinical risk factor** (refer to Appendix 1AB) OR **Unvaccinated ATSI** patient AND age **greater than 35 years** WITH at least one **recognised clinical risk factor** (refer to Appendix 1AB) *There is a cumulative increase in risk of progression to severe disease with each additional risk factor, which may further impact eligibility at times of extreme product shortage.*
	PREGNANT WOMEN IN SECOND OR THIRD TRIMESTER	**Unvaccinated or vaccinations not up to date** OR **Fully vaccinated** AND **immunocompromised** (refer to Appendix 1B and Appendix 1C)
	SEVERE IMMUNO-COMPROMISED STATE	**Severe immunocompromise** (refer to Appendix 1B) regardless of age or vaccination status
	PAEDIATRIC PATIENTS	**Paediatric Infectious Diseases Specialist review** required (PCH) to determine appropriateness of adolescent risk factors. *NB. Patients within 2 years of receiving Hematopoietic Stem-Cell Transplantation (HSCT) or Solid Organ Transplant, regardless of vaccination status will be prioritised.*
TIER 2	**UNVACCINATED OR VACCINATIONS NOT UP TO DATE AND AT HIGH RISK FOR SEVERE DISEASE**	**Unvaccinated** AND age **greater than 55 years** (or **ATSI patients ≥ 35 years**) OR **Vaccinations not up to date** AND age **greater than 55 years** WITH at least one other **recognised clinical risk factor** (refer to Appendix 1AB) OR **Unvaccinated or vaccinations not up to date** AND **moderate immunocompromise** (refer to Appendix 1C), regardless of age or recognised clinical risk factors
	PREGNANCY	**Unvaccinated** OR **Vaccinations not up to date** WITH at least one **recognised clinical risk factor** (refer to Appendix 1AB) NB. Gestational diabetes requiring medication therapy is also included as a risk factor in addition to Appendix 1AB for this patient group Limited data pertaining to use in 1st trimester – clinical benefit/risk assessment should be undertaken
	PAEDIATRIC PATIENTS	**Paediatric Infectious Diseases Specialist (PCH) review** required and referral of unvaccinated or partially vaccinated adolescents with paediatric clinical risk factors (refer to Appendix 1D)
TIER 3	**MODERATE RISK OF PROGRESSION TO SEVERE DISEASE**	**Unvaccinated** or **vaccinations not up to date** AND **less than 55 years** WITH at least one other **recognised clinical risk factor** (refer to Appendix 1AB) OR **Moderate immunocompromise** (refer to Appendix 1C), regardless of age or vaccination status OR **Vaccinations not up to date** AND ≥ 55 years (or ATSI ≥ 35 years) regardless of any recognised risk factors

APPENDIX 1AB

RECOGNISED CLINICAL RISK FACTORS FOR DISEASE PROGRESSION (per COMET-ICE trial) ADAPTED FROM COMET-ICE CRITERIA FOR UNVACCINATED ADULTS AND ADULTS AT HIGH RISK OF SEVERE DISEASE
Age ≥ 55 years
Chronic kidney disease (eg eGFR < 60)
Chronic obstructive pulmonary disease (includes history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion)
Chronic heart failure (NYHA class II or greater)
Diabetes (requiring pharmacological treatment)
Moderate to severe asthma (on regular inhaled steroid therapy or prescribed a course of oral steroids within past 12 months for management of asthma)
Obesity (BMI ≥ 30 kg/m^2)

APPENDIX 1B

APPENDIX 1C

SEVERE IMMUNOCOMPROMISE STATUS	MODERATE IMMUNOCOMPROMISE STATUS
Subset of immunocompromised persons as per ATAGI Recommendations on the use of a 3rd primary dose of COVID-19 vaccine in individuals who are severely immunocompromised	

• Patients who are within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
• Patients receiving Bruton tyrosine kinase inhibitors
• Chimeric antigen receptor T cell recipients
• Post-hematopoietic stem cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
• Patients with hematologic malignancies who are on active therapy
• Lung transplant recipients
• Patients who are within 1 year of receiving a solid-organ transplant (other than lung transplant) or haematopoietic stem cell transplant
• Solid-organ transplant recipients with recent treatment for acute rejection with T or B cell depleting agents
• Patients with certain primary immunodeficiencies
  ○ PIDs affecting cellular and humoral immunity (severe and other combined immunodeficiencies (https://doi.org/10.1007/s10875-019-00737-x)
  ○ PIDs with profoundly decreased or absent B cell number or function
  ○ PIDs with impaired interferon responses
• Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm^3
• Patients on any of the following agents not already listed
  ○ Anti-CD20 antibodies rituximab, obinutuzumab, ocrelizumab, ofatumumab
  ○ BTK inhibitors ibrutinib, acalabrutinib, zanubrutinib
  ○ Sphingosine 1- phosphate receptor modulators fingolimod, siponimod
  ○ Anti-CD52 antibodies alemtuzumab
  ○ Anti-complement antibodies eculizumab
  ○ Anti-thymocyte globulin
	○ Primary immunodeficiency including combined immunodeficiency and syndromes, major antibody deficiency (e.g. common variable immune deficiency (CVID) or agammaglobulinemia), defects of innate immunity (including phagocytic cells), defects of immune regulation, complement deficiencies and phenocopies of primary immunodeficiencies
	○ Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes
	○ Solid organ transplant on immunosuppressive therapy
	○ Greater than 12 months post-transplant: solid organ transplant (on immunosuppressive therapy) or haematopoietic stem cell transplant.
	○ Advanced or untreated HIV with CD4 counts <200/microL, or those with a higher CD4 count unable to be established on effective anti-retroviral therapy, recent (within 12 months) AIDS-defining condition, or persistent/recurrent viraemia OR not on ART (excluding elite controllers).
	○ Haemodialysis or peritoneal dialysis
	○ Immunosuppressive therapy (current or recent) examples include:
	  ○ Chemotherapy or radiotherapy
	  ○ JAK inhibitors - tofacitinib, baricitinib, ruxolitinib
	  ○ High-dose corticosteroids (≥20 mg of prednisone per day, or equivalent) for ≥14 days in a month, or pulse corticosteroid therapy
	○ Biologic and targeted therapies that are anticipated to reduce the immune response to COVID-19 vaccine
	○ Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDS) including mycophenolate, methotrexate (>0.4 mg/kg/week), leflunomide, azathioprine (≥ 3mg/kg day), 6-mercaptopurine (≥ 1.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus).

APPENDIX 1D

PAEDIATRIC CLINICAL RISK FACTORS
• paediatric chronic complex condition, • obesity (>95th centile for age and gender based on CDC growth charts), • severe asthma, • chronic obstructive lung disease, • diabetes (on insulin), • severe cardiac disease, • end stage renal disease, • sickle cell disease, PA • immune deficiency

ADDITIONAL INFORMATION

AGENTS THAT ARE NOT CONSIDERED TO IMPART ANY INCREASED IMMUNOSUPPRESSIVE RISK
▪ Anti-integrins natalizumab, vedolizumab ▪ Anti-TNF-α antibodies infliximab, adalimumab, etanercept, golimumab, certolizumab ▪ Anti-IL1 antibodies anakinra ▪ Anti-IL6 antibodies tocilizumab ▪ Anti-IL17 antibodies secukinumab, ixekizumab ▪ Anti-IL4 antibodies dupilumab Anti-IL23 antibodies ustekinumab ▪ Immune checkpoint inhibitors nivolumab, pembrolizumab, ipilimumab, atezolizumab

DEFINING VACCINATION STATUS (as per current ATAGI statement February 2022)			
Patient Group	**Unvaccinated**	**Vaccinations not up to date (eg Partially Vaccinated)**	**Up to Date or Fully Vaccinated**
General Population (immunocompetent, including pregnant patients)	Patient has not received a TGA approved or other recognised COVID-19 vaccine	Patient has received only 1 dose of a TGA approved or other recognised vaccine	Patient has received 2 doses (considered a primary course) of a TGA approved or other recognised vaccine
Immunocompromised patients (moderate-severely immunocompromised)	Patient has not received a TGA approved or other recognised COVID-19 vaccine	Patient has received only 1 or 2 doses of a TGA approved or other recognised vaccine	Patient has received 3 doses of a TGA approved or other recognised vaccine
Individuals with evidence of previous SARS-CoV-2 infection	Patient has not received a TGA approved or other recognised COVID-19 vaccine	Individuals with previous COVID-19 infection are still recommended to complete their vaccination schedule. Evidence suggests that prior infection with Delta or other variants is not completely protective against re-infection with Omicron. ATAGI recommends boost doses for all individuals with previous COVID-19. If infected with COVID-19 prior to commencing vaccination or during vaccination schedule the next dose can be deferred for up to 4 months.	

APPENDIX 2A

REMDESIVIR - POTENTIAL DRUG INTERACTIONS					
ADVICE ▪ These are theoretical interactions only, co-administration of these agents has NOT been studied ▪ As a precaution any potentially interacting therapies listed should be withheld or avoided temporarily where possible					
	CYP2C8 inhibitors	**CYP2D6 inhibitors**	**CYP3A4 inhibitors**	**P-gp inhibitors**	**OATP1B1 inhibitors**
Interactions that may ↑ remdesivir levels	Clopidogrel^{+++} Gemfibrozil^{+++} trimethoprim	amiodarone bupropion^{+++} celecoxib, cinacalcet^{++}, cobicistat duloxetine^{++} fluoxetine^{+++} haloperidol methadone, metoclopramide, midodrine, mirabegron^{++} paroxetine^{+++} terbinafine^{+++}	amiodarone, aprepitant^{++}, atazanavir^{++} ciclosporin^{++}, ciprofloxacin^{++}, clarithromycin^{+++}, cobicistat^{+++} darunavir, diltiazem^{++} erythromycin^{++} fluconazole^{++}, fluvoxamine^{++} imatinib, isavuconazole, itraconazole^{+++}, ketoconazole^{+++} letermovir^{++}, lopinavir palbociclib, posaconazole^{+++} quinine ribociclib, ritonavir^{+++} saquinavir tacrolimus, ticagrelor, verapamil^{++}, verapamil^{+++}	amiodarone, azithromycin carvedilol, ciclosporin, clarithromycin, cobicistat erythromycin, everolimus glecaprevir with pibrentasvir isavuconazole, itraconazole ketoconazole lapatinib, ledipasvir osimertinib ritonavir ticagrelor, tolvaptan vandetanib, velpatasvir, vemurafenib, venetoclax, verapamil, voxilaprevir	atazanavir, clarithromycin cyclosporine erythromycin gemfibrozil lopinavir rifampicin, ritonavir simepravir
	CYP2C8 inducers	**CYP2D6 inducers**	**CYP3A4 inducers**	**P-gp inducers**	**OATP1B1 inducers**
Interactions that may ↓ remdesivir levels	rifampicin $^{++}$	dexamethasone rifampicin haloperidol	apalutamide^{+++}, aprepitant bosentan^{++} carbamazepine^{+++}, clobazam, corticosteroids (eg dexamethasone, prednisolone, hydrocortisone) dabrafenib efavirenz^{++}, encorafenib, enzalutamide^{+++}, etravirine^{++} lorlatinib^{++}, lumacaftor^{+++} modafinil^{++} nevirapine phenobarbitone, phenytoin^{+++} rifabutin, rifampicin^{+++}, ritonavir St John's Wort^{+++} tipranavir, topiramate vemurafenib	apalutamide carbamazepine lorlatinib phenytoin rifampicin St John's Wort tipranavir	No OATP inducers have been identified

REMDESIVIR - POTENTIAL DRUG INTERACTIONS		
	CYP3A4 substrates (levels may potentially be ↑ or ↓ by remdesivir)	**OATP1 B1 / B3 substrates**
Drug that may have their levels ↑ by concurrent administration of remdesivir	abiraterone, alprazolam, amitriptyline, apalutamide, apixaban, aprepitant, aripiprazole, atorvastatin betamethasone, bictegravir, bortezomib, brentuximab, budesonide carbamazepine, ciclosporin, cinacalcet, clarithromycin, clopidogrel, cobicistat, codeine, colchicine, cyclophosphamide dabrafenib, darunavir, dasatinib, dexamethasone, diazepam, diltiazem, docetaxel, domperidone, donepezil elvitegravir, encorafenib, enzalutamide, eplerenone, erythromycin, esomeprazole, etoposide, etravirine, everolimus felodipine, fentanyl, haloperidol, hydrocortisone ibrutinib, ifosfamide, imatinib, irinotecan, isavuconazole, itraconazole, ivabradine, ivacaftor ketoconazole lercanidipine, lidocaine, lopinavir, lorlatinib, lurasidone methylprednisolone, midazolam, midostaurin, mirabegron, mirtazapine nifedipine, nilotinib, nimodipine omeprazole, ondansetron, oxycodone paclitaxel, palbociclib, pazopanib, pomalidomide, propranolol quetiapine, quinine reboxetine, ribociclib, rifabutin, rilpivirine, risperidone, ritonavir, rivaroxaban, romidepsin, ruxolitinib sildenafil, simvastatin, sirolimus, solifenacin, sorafenib, sunitinib tacrolimus, tadalafil, tamoxifen, ticagrelor, tofacitinib, tolvaptan, tramadol vandetanib, velpatasvir, vemurafenib, venetoclax, venlafaxine, verapamil, vinblastine, vincristine, vinorelbine, voriconazole, voxilaprevir warfarin (R-isomer) ziprasidone, zolpidem	atorvastatin bosentan digoxin empagliflozin, ezetimibe fexofenadine, fluvastatin glecaprevir, grazoprevir levothyroxine methotrexate olmesartan pravastatin rifampicin, rifaximin, rosuvastatin simvastatin telmisartan valsartan, velpatasvir, voxilaprevir

	CYP1A2 substrates
Drugs that may have their levels ↓ by concurrent administration of remdesivir	agomelatine, amitriptyline, asenapine, axitinib bendamustine clopidogrel, clozapine duloxetine erlotinib fluvoxamine haloperidol imipramine lidocaine melatonin olanzapine, ondansetron paracetamol, pomalidomide, propranolol rasagiline, ropinirole, ropivacaine stiripentol tamoxifen, theophylline warfarin (R-isomer) zolmitriptan

APPENDIX 2B

CORTICOSTEROIDS (SYSTEMIC) - POTENTIAL DRUG INTERACTIONS	
ADVICE ▪ As a precaution any potentially interacting therapies listed should be withheld or avoided temporarily where possible	
Interactions that may ↑ corticosteroid levels	**CYP3A4 inhibitors**
	amiodarone, aprepitant^{++}, atazanavir^{++} ciclosporin^{++}, ciprofloxacin^{++}, clarithromycin^{+++}, cobicistat^{+++} darunavir, diltiazem^{++} erythromycin^{++} fluconazole^{++}, fluvoxamine^{++} imatinib, isavuconazole, itraconazole^{+++}, ketoconazole^{+++} letermovir^{++}, lopinavir palbociclib, posaconazole^{+++} quinine ribociclib, ritonavir^{+++} saquinavir tacrolimus, ticagrelor, verapamil^{++}, verapamil^{+++}
Interactions that may ↓ corticosteroid levels	**CYP3A4 inducers**
	apalutamide^{+++}, aprepitant bosentan^{++} carbamazepine^{+++}, clobazam, corticosteroids (eg dexamethasone, prednisolone, hydrocortisone) dabrafenib efavirenz^{++}, encorafenib, enzalutamide^{+++}, etravirine^{++} lorlatinib^{++}, lumacaftor^{+++} modafinil^{++} nevirapine phenobarbitone, phenytoin^{+++} rifabutin, rifampicin^{+++}, ritonavir St John's Wort^{+++} tipranavir, topiramate vemurafenib

APPENDIX 2C

BARICITINIB - POTENTIAL DRUG INTERACTIONS

ADVICE

- Majority of these are theoretical interactions only
- Extensive study of their concurrent administration together has not been performed. In the limited studies performed no clinically significant impact on drug levels has been observed.
- As a precaution any potentially interacting therapies listed should be withheld or avoided temporarily where possible

	CYP3A4 inhibitors	OAT3 inhibitors*	BCRP inhibitors*	P-gp inhibitors	MATE2-K inhibitors*
Interactions that may ↑ baricitinib levels	amiodarone, aprepitant^{++}, atazanavir^{++} ciclosporin^{++}, ciprofloxacin^{++}, clarithromycin^{+++}, cobicistat^{+++} darunavir, diltiazem^{++} erythromycin^{++} fluconazole^{++}, fluvoxamine^{++} imatinib, isavuconazole, itraconazole^{+++} ketoconazole^{+++} letermovir^{++}, lopinavir palbociclib, posaconazole^{+++} quinine ribociclib, ritonavir^{+++} saquinavir tacrolimus, ticagrelor, verapamil^{++}, verapamil^{+++}	balsalazide cabotegravir ethacrynic acid irbesartan ketorolac nitazoxanide probenecid rifampicin valsartan	curcumin cyclosporin eltrombopag	amiodarone, azithromycin carvedilol, ciclosporin, clarithromycin, cobicistat erythromycin, everolimus glecaprevir with pibrentasvir isavuconazole, itraconazole ketoconazole lapatinib, ledipasvir osimertinib ritonavir ticagrelor, tolvaptan vandetanib, velpatasvir, vemurafenib, venetoclax, verapamil, voxilaprevir	cimetidine ciprofloxacin dolutegravir isavuconazole nizatidine pyrimethamine trimethoprim vandetanib
*very limited evidence exists for these potential interactions and their clinical significance					
	CYP3A4 inducers	**OAT3 inducers**	**BCRP inducers**	**P-gp inducers**	**MATE2-K inducers**
Interactions that may ↓ baricitinib levels	apalutamide^{+++}, aprepitant bosentan^{++} carbamazepine^{+++}, clobazam, corticosteroids (eg dexamethasone, prednisolone, hydrocortisone) dabrafenib efavirenz^{++}, encorafenib, enzalutamide^{+++}, etravirine^{++} lorlatinib^{++}, lumacaftor^{+++} modafinil^{++} nevirapine phenobarbitone, phenytoin^{+++} rifabutin, rifampicin^{+++}, ritonavir St John's Wort^{+++} tipranavir, topiramate vemurafenib	There is limited information available relating to OAT3 inducers	There is limited information available relating to BCRP inducers	apalutamide carbamazepine lorlatinib phenytoin rifampicin St John's Wort tipranavir	There is limited information available relating to MATE2-K inducers

APPENDIX 2D

NIRMATRELVIR plus RITONAVIR (PAXLOVID®)
CLINICALLY SIGNIFICANT DRUG INTERACTIONS

CLINICAL PEARLS

- Nirmatrelvir and ritonavir are BOTH inhibitors of the CYP3A enzyme and also substrates for this enzyme
- Additionally, ritonavir is a strong inhibitor of the enzymes CYP3A4 > CYP2D6 > CYP2C9 / CYP2C19 > CYP2A6 / CYP1A2 / CYP2E1 plus P-gp
- Nirmatrelvir is a likely inhibitor of P-gp, MATE1 and OATP1B1
- Ritonavir is a strong inducer of the enzymes CYP1A2, CYP2C8, CYP2C9 and CYP2C19
- As a precaution any potentially interacting therapies listed should be withheld or avoided temporarily where possible

DRUGS THAT INTERACT WITH PAXLOVID®

	CYP3A4 substrates	CYP2D6 substrates	CYP2C9/2C19 substrates	OTHERS	P-gp substrates
ABSOLUTELY CONTRAINDICATED **Drugs that will have their levels INCREASED and WILL cause SERIOUS TOXICITY from co-administration with PAXLOVID®**	ABEMACICLIB, ACALABRUTINIB, ALFUZOSIN, AMIODARONE, AVANAFIL, BOSENTAN, CERITINIB, CICLOSPORIN, CLARITHROMYCIN, CLOPIDOGREL, COLCHICINE DASATINIB, DIAZEPAM, DISOPYRAMIDE, DOMPERIDONE ELETRIPTAN, EPLERENONE, ERGOMETRINE, ERGOTAMINE, ERYTHROMYCIN, EVEROLIMUS FELODIPINE IBRUTINIB, ISAVUCONAZOLE, IVABRADINE LAPATINIB, LERCANIDIPINE, LORLATINIB, LURASIDONE METHYLPREDNISOLONE, MODAFINIL NERATINIB, NILOTINIB PETHIDINE QUINIDINE, QUININE RIBOCICLIB, RIVAROXABAN SILDENAFIL, SIROLIMUS, SORAFENIB, TACROLIMUS, TADALAFIL, TICAGRELOR, VARDENAFIL, VENETOCLAX, VINBLASTINE, VINCRISTINE, VORICONAZOLE	BORTEZOMIB CLOZAPINE FLECAINIDE	BOSENTAN DIAZEPAM PIROXICAM VORICONAZOLE	CLOZAPINE (1A2)	CICLOSPORIN, CLOPIDOGREL EVEROLIMUS GLECAPREVIR/PIBRENTASVIR SIROLIMUS
Drugs that will REDUCE the effectiveness of PAXLOVID®	**CYP3A INDUCERS**	APALUTAMIDE, APREPITANT, ARMODAFINIL BOSENTAN CARBAMAZEPINE DABRAFENIB EFAVIRENZ, ENCORAFENIB, ENZALUTAMIDE, ETRAVIRINE LORLATINIB, LUMACAFTOR MODAFINIL NEVIRAPINE PHENOBARITAL, PHENYTOIN RIFABUTIN, RIFAMPICIN, RUFINAMIDE ST JOHN'S WORT TIPRANAVIR VEMURAFENIB			

ADVICE – do not co-administer Paxlovid® with these agents due to **high risk** for serious toxicity which may arise.
Ceasing these medications may not completely overcome the risk due to different factors including significance of the potential toxicity, prolonged half-life of the affected drugs, narrow therapeutic index or potential to reduce the efficacy of Paxlovid®.
Recommendation is to select an alternative COVID-19 therapy in place of Paxlovid® (Nirmatrelvir-Ritonavir)

	CYP3A4 substrates	CYP2D6 substrates	CYP2C9/2C19 substrates	OTHERS	P-gp substrates
CONTRAINDICATED **Drugs that will have their levels INCREASED and LIKELY to cause SERIOUS TOXICITY from co-administration with PAXLOVID®**	ATORVASTATIN ENCORAFENIB ITRACONAZOLE KETOCONAZOLE RUXOLITINIB SIMVASTATIN SUNITINIB		ROSUVASTATIN RUXOLITINIB		
ADVICE – suggestion is to avoid co-administration of these agents with Paxlovid® due to high likelihood for serious toxicity to occur. **Alternative choice of COVID-19 therapy is recommended** however if treatment using Paxlovid® is considered a priority and alternative agents deemed unsuitable, then either stop or substitute the interacting medication/s temporarily during treatment with Paxlovid® and only restart in 3 to 5 days after completing course of Paxlovid®					
USE WITH CAUTION **Drugs that will have their levels INCREASED and be AT RISK of causing TOXICITY from co-administration with PAXLOVID®**	ALPRAZOLAM, APIXABAN , ATAZANAVIR DARIFENACIN, DARUNAVIR, DEXAMETHASONE FENTANYL, FOSAMPRENAVIR LIDOCAINE MACITENTAN, METHADONE, MIDAZOLAM NIFEDIPINE PREDNISOLONE QUETIAPINE RIFABUTIN, RISPERIDONE SAXAGLIPTIN, SOLIFENACIN VERAPAMIL WARFARIN (R-ISOMER) ZOLPIDEM, ZOPICLONE	ARIPIPRAZOLE DARIFENACIN LIDOCAINE HALOPERIDOL METHADONE, MORPHINE (VIA CODEINE) OXYCODONE PALIPERIDONE, PERHEXILINE, PROPRANOLOL TAMOXIFEN, TRAMADOL		LIDOCAINE (1A2) METHADONE (1A2)	AFATINIB, APIXABAN DABIGATRAN , DIGOXIN PREDNISOLONE
ADVICE – co-administration of these agents with Paxlovid® will likely result in risk of toxicity to occur and therefore not recommended. **An attempt to select an alternative COVID-19 treatment is recommended.** If alternative treatment options are unsuitable then either stop or replace the interacting medication/s temporarily during treatment with Paxlovid® and only restart in 3 to 5 days after completing course of Paxlovid®					

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