Oral antiviral agents for SARS-CoV2

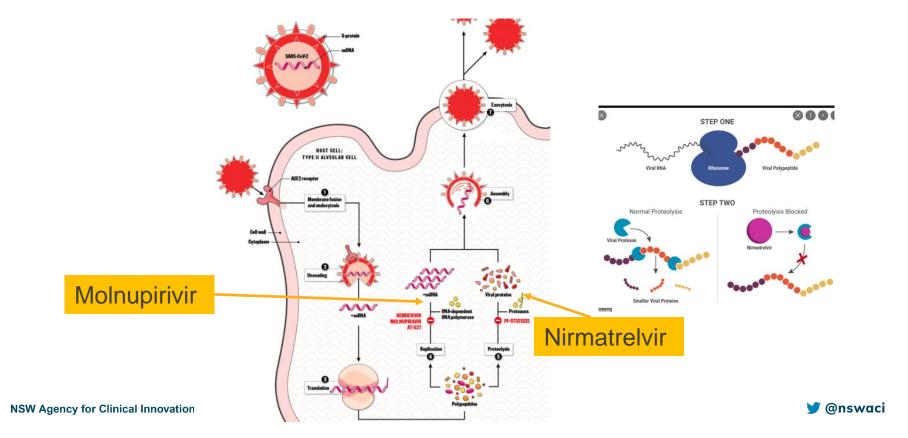
Prof Peter Wark, ACI NSW Health





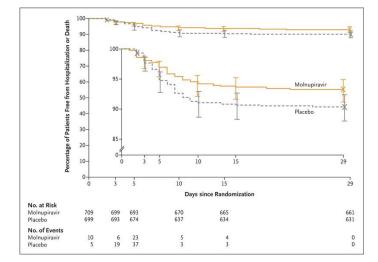


Antiviral mechanisms of action



Molnupirivir or Lagevrio

- RCT 1433
 - >18yrs
 - all unvaccinated
 - At least 1 risk factor severe COVID-19
 - Within 5 days of infection
- Randomised Molnupirivir 800mg BD or placebo for 5 days
- molnupiravir (28 of 385 participants [7.3%])
 than with placebo (53 of 377 [14.1%])
 (difference, -6.8 percentage points; 95%
 confidence interval, -11.3 to -2.4; P=0.001)
- Relative risk reduction, 48%, NNT 15
- no serious side-effects



Subgroup	Molnupiravir no. of events/no.	Placebo	Absolute Risk Reduction (95% CI) percentage points	
Sex	no. oj evenis/no.	oj pariicipanis	percentage poin	113
Female	16/379	27/344	⊢	-3.6 (-7.4 to -0.2)
Male	32/330	41/355		-1.9 (-6.5 to 2.8)
Days since onset of symptoms				(,
≤3	25/339	28/335	⊢ •	-1.0 (-5.2 to 3.2)
>3	23/370	40/364		-4.8 (-9.0 to -0.7
Baseline Covid-19 severity				
Mild	19/395	27/376	 i	-2.4 (-5.9 to 1.0)
Moderate	29/311	40/321		-3.1 (-8.1 to 1.8)
Baseline SARS-CoV-2 nucleocapsid antibody	status			
Positive	5/136	2/146		2.3 (-1.7 to 7.1)
Negative	39/541	64/520		-5.1 (-8.8 to -1.6
Risk factors for severe Covid-19				
>60 yr of age	12/118	16/127		-2.4 (-10.6 to 5.8
Obese	29/535	46/507	H=-6	-3.7 (-6.9 to -0.5
Diabetes mellitus	17/107	17/117	- i-	1.4 (-8.2 to 11.1
Serious heart condition	8/86	9/78		-2.2 (-12.4 to 7.5
Race				
American Indian or Native American	18/207	21/199		-1.9 (-7.8 to 4.0)
Asian	7/25	7/23	• :	-2.4 (not calculat
Black	10/157	15/142		-4.2 (-11.1 to 2.2)
White	29/556	54/573	⊢• →	-4.2 (-7.3 to -1.2)
Baseline SARS-CoV-2 qualitative assay				
Detectable	45/614	61/613	 >	-2.6 (-5.8 to 0.5)
Undetectable	0/54	0/51		0.0 (-7.1 to 6.7)
Unknown	3/41	7/35		-12.7 (-29.9 to 2.9
		-30	-20 -10 0 10	20
		-		-

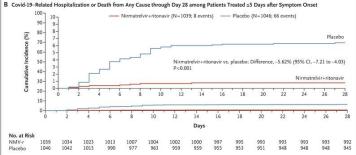


Nirmaltrevir/Ritonavir or Paxlovid

- RCT 2246 people
 - >18yrs
 - all unvaccinated
 - At least 1 risk factor severe COVID-19
 - Within 5 days of infection
- Hospitalization or death by d28 lower in the nirmatrelvir group vs placebo by 6.32 %(95%CI; -9.04 to -3.59; P<0.001
- relative risk reduction, 89.1%, NNT 16
- The viral load lower with at day 5 of treatment, adjusted mean difference of -0.868 log₁₀

Hammond et al NEJM 2021;





Subgroup	Nirmatrelvir+Ritonavir	Placebo	Difference from Placel	oo (95% CI)
	no. of events/total no.		percentage points	
Overall	8/1039	66/1046	₩ .	-5.62 (-7.21 to -4.03)
Time since symptom onset			1	
≤3 days	5/697	44/682	⊢ ⊷ ;	-5.81 (-7.78 to -3.84)
>3 days	3/342	22/364	⊢ → ;	-5.23 (-7.91 to -2.55)
Age				
<65 yr	7/908	46/909		-4.35 (-5.91 to -2.79)
≥65 yr	1/131	20/137		-13.93 (-20.07 to -7.80
Sex	35	50		
Male	4/520	41/540		-6.93 (-9.32 to -4.53)
Female	4/519	25/506	→ :	-4.23 (-6.29 to -2.17)
Body-mass index	2	- 0		
<25	1/209	9/207	⊢	-3.88 (-6.83 to -0.94)
25 to <30	3/458	28/466	i	-5.44 (-7.75 to -3.13)
≥30	4/371	29/373		-6.85 (-9.82 to -3.87)
Diabetes mellitus				
Yes	2/125	9/127		-5.51 (-10.51 to -0.52
No	6/913	57/919	H-1	-5.63 (-7.30 to -3.96)
Baseline SARS-CoV-2 serology status			1	
Negative	7/487	58/505	⊢ • · · · · ·	-10.25 (-13.28 to -7.21
Positive	1/540	8/528	 • 	-1.34 (-2.45 to -0.23)
Received or expected to receive Covid-19 monoclonal antibody treatment		70		
Yes	1/70	2/69	⊢ • • •	→ -1.51 (-6.40 to 3.37)
No	8/1039	66/1046		-5.62 (-7.21 to -4.03)



Contraindications

Molnupiravir (LAGEVRIO)

not recommended in pregnancy and breastfeeding. It is recommended that sexually active women of childbearing potential use contraception and men also use contraception during and 3 months after treatment with LAGEVRIO.

https://www.tga.gov.au/media-release/tga-provisionally-approves-two-oral-covid-19-treatments-molnupiravir-lagevrio-and-nirmatrelvir-ritonavir-paxlovid



Contraindications

Nirmaltrevir-Ritonavir (PAXLOVID)

- not recommended in pregnancy or breastfeeding, and in women of childbearing potential. It is recommended that sexually active women of childbearing potential use contraception.
- Not in severe renal disease eGFR<30ml/min (dose reduction 30-60ml/min)
- Not is severe liver disease

Medicinal product class	Medicinal products within class			
Interactions that result in an increase or decrease in concentrations of concomitant medicine				
Alpha 1-adrenoreceptor antagonist	alfuzosin			
Antianginal	ranolazine			
Antiarrhythmics	amiodarone, flecainide			
Anticancer	neratinib, venetoclax			
Anti-gout	colchicine			
Antipsychotics	lurasidone, clozapine			
Ergot derivatives	ergometrine			
Lipid-modifying agents HMG-CoA reductase inhibitors	simvastatin			
Nonsteroidal anti-inflammatory drugs (NSAIDs)	piroxicam			
Opioid analgesic	pethidine			
PDE5 inhibitor	avanafil, sildenafil, vardenafil, tadalafil			
Sedative/hypnotics	diazepam			



Anti-SARS-CoV-2 Monoclonal antibodies & antivirals

Expanding the model of care

Care in Community CoP | 10 February 2022

Ellen Rawstron







Overview

- NSW Monoclonal antibody model of care updated for oral antivirals
- Defines eligibility & priority cohorts
 - Clinical consensus
 - Considerations = those most at risk & supply
- Recommendations for adults and adolescents (Table 1 and Table 2)
- Decision Flow Charts (Figures 1, 2, 3)
- To be used with CEC & NSW Health Care in Community Guidance
- Available via NSW Health and ACI websites at https://aci.health.nsw.gov.au/covid-19/communities-of-practice



Eligibility in NSW

- Within 5 days of symptom onset AND
- No oxygen requirement due to COVID-19 AND
- Reduced immunity to COVID-19 by being:
 - unvaccinated (i.e. received no doses of a COVID-19 vaccination) OR
 - not fully vaccinated (i.e. has not completed their primary course of COVID-19 vaccination) OR
 - overdue for booster (as per ATAGI guidance) OR
 - Immunocompromised* (irrespective of age and vaccine status)
- Medicine-specific age and risk factors (as outlined in Table 1 or Table 2).



^{*}Immunocompromised defined as per ATAGI guidance.

Table 1. NSW-specific risk factors for high priority cohorts in adults

Risk factors that must be met for prescription of any of the four medications

- Within 5 days of symptom onset AND
- No oxygen requirement due to COVID-19 AND
- · Reduced immunity to COVID-19 by being:
 - unvaccinated (i.e. received no doses of a COVID-19 vaccination) OR
 - not fully vaccinated (i.e. has not completed their primary course of COVID-19 vaccination) OR
 - overdue for booster (as per ATAGI guidance) OR
 - immunocompromised* AND
- · Medicine-specific age and risk factors outlined below

Medication-specific risk factor/s

Sotrovimab

- . Pregnant women in their second or third trimester OR
- Age ≥ 65 years or ≥35 years if Aboriginal and/or Torres Strait Islander (excluding pregnant women)

AND one of the following risk factors:

- Obesity (BMI ≥ 30 kg/m2)
- · Severe cardiovascular disease (including hypertension)
- Severe chronic lung disease; including severe asthma (requiring a course of oral steroids in the previous 12 months),
 COPD and interstitial lung disease
- Type 1 or 2 diabetes mellitus
- Severe chronic kidney disease, including those that are on dialysis
- · Severe chronic liver disease
- Immunocompromised*



Medication-specific risk factor/s

Nirmatrelvir plus ritonavir

Non-pregnant adults who are aged ≥ 65 years or ≥35 years if Aboriginal and/or Torres Strait Islander

AND one of the following risk factors:

- Obesity (BMI ≥ 30 kg/m2)
- Severe cardiovascular disease (including hypertension)
- Severe chronic lung disease; including severe asthma (requiring a course of oral steroids in the previous 12 months),
 COPD and interstitial lung disease
- · Type 1 or 2 diabetes mellitus

OR aged ≥18 years if immunocompromised*

Molnupiravir

Non-pregnant adults who are aged ≥ 65 years or ≥35 years if Aboriginal and/or Torres Strait Islander

AND one of the following risk factors:

- Obesity (BMI ≥ 30 kg/m2)
- · Severe cardiovascular disease (including hypertension)
- Severe chronic lung disease; including severe asthma (requiring a course of oral steroids in the previous 12 months),
 COPD and interstitial lung disease
- Type 1 or 2 diabetes mellitus
- · Severe chronic kidney disease, including those who are on dialysis and unable to receive monoclonal antibody treatment
- · Severe chronic liver disease

OR aged ≥18 years if immunocompromised*



Table 2. NSW-specific risk factors for adolescents

Risk factors that must be met for prescription in adolescents

- Aged 12 to 17 years AND
- Weighing at least 40kg AND
- Within 5 days of symptom onset AND
- No oxygen requirement due to COVID-19 AND
- · Reduced immunity to COVID-19 by:
 - unvaccinated (i.e. received no doses of a COVID-19 vaccination) OR
 - partially vaccinated (i.e. only 1 dose of COVID-19 vaccine) OR
 - immunocompromised (as per ATAGI quidance), irrespective of vaccine status AND
- · Medication-specific age and risk factors outlined below

Medication-specific risk factors

Sotrovimab

AND at least **two** of the following risk factors::

- Paediatric complex chronic condition (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic and neuromuscular
- Diabetes (requiring medication) and pre-gestational diabetes (requiring medication) in pregnant women
- Obesity (BMI ≥ 95th centile for age)
- Chronic kidney disease (GFR <15 mL/min/1.73m2)
- Heart failure, or Congenital Heart Disease with persisting cyanosis or pulmonary hypertension
- Chronic obstructive lung disease (e.g. chronic lung disease requiring oxygen, cystic fibrosis with reduced lung function)
- Severe asthma (in the past 12 months: ≥1 exacerbation requiring ICU admission OR IV treatment OR ≥2 hospital admissions for asthma)

In other exceptional circumstances, please discuss eligibility with a paediatric infectious diseases specialist.



Figure 1. Decision pathway: outpatient suitability for monoclonal antibodies or oral antivirals

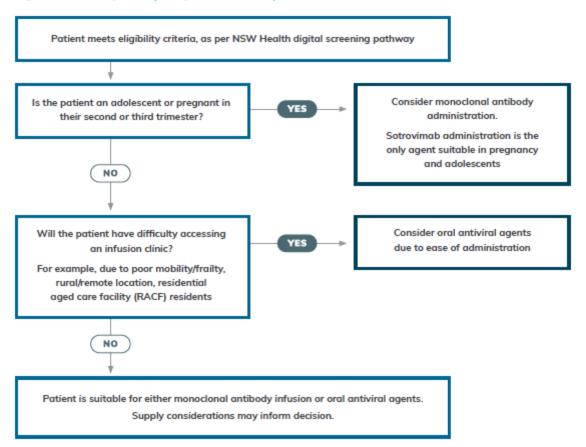
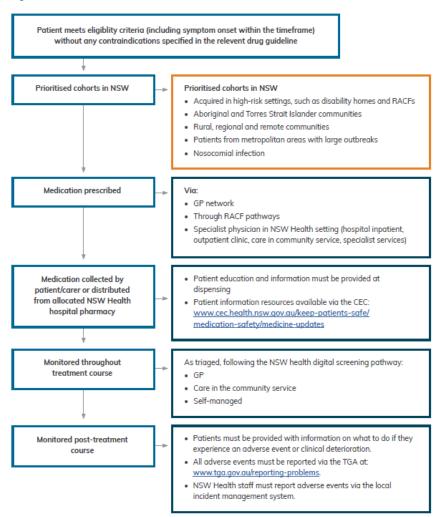


Figure 3: Flowchart for administration of oral antivirals in adults with mild and moderate COVID-19









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