South African National Department of Health
Evidence Summary
Component: COVID-19

TITLE: Should nirmatrelvir+RTV be used to treat confirmed COVID-19?

Date: 14 March 2022

Key findings

- We reviewed the evidence for the efficacy and safety of nirmatrelvir plus ritonavir (nirmatrelvir+RTV) compared to placebo or standard or care for treating COVID-19. We identified one trial reporting on this intervention.
- We identified one phase 2-3, blinded, randomized placebo-controlled clinical trial in symptomatic, unvaccinated, non-hospitalised adults at high risk for progression to severe COVID-19 (i.e. adults with at least one condition or co-morbidity that put them at risk of severe COVID-19) (Hammond et al., 2022). The trial randomized 2246 to either nirmaltrelvir+ritonavir 12 hourly for 5 days (n = 1120) or placebo (n = 1126).
- Nirmatrelvir+RTV likely reduced mortality in unvaccinated, non-hospitalised adult patients at high risk of progression to severe COVID-19, if treatment was initiated within 5 days of symptom onset: 0/1120 deaths in the nirmatrelvir+RTV group compared to 12/1126 in the placebo group. The absolute risk reduction (ARR) of 1.07% (95% CI 0.47 to 1.67%) favours nirmatrelvir+RTV (moderate certainty evidence).
- Nirmatrelvir+RTV reduced hospitalisation in unvaccinated, non-hospitalised adult patients at high risk of progression to severe COVID-19, if treatment was initiated within 5 days of symptom onset: 8/1120 hospitalisations in the nirmatrelvir+RTV group compared to 65/1126 in the placebo group (ARR 5.15%; 95% CI 3.69 to 6.61%, high certainty evidence)
- The risk of adverse events was similar between the two groups: 476/1109 (22.6%) experienced an adverse event in the nirmatrelvir+RTV group and 525/1115 (23.9%) in the placebo group (RR 0.91; 95% CI 0.83 to 1.00, moderate certainty evidence). Serious adverse events occurred less frequently in the nirmatrelvir+RTV group (18/1109, 1.6%) than the placebo group (74/1115, 6.6%) (RR 0.24; 95% CI 0.15 to 0.41, high certainty evidence).
- Efficacy and safety in other patient groups (e.g. vaccinated, hospitalised, children, pregnant women, HIV-infected with unsuppressed viral load, and those at lower risk for severe disease) is unknown. Overall nirmaltrelvir+ritonavir reduced the study composite endpoint of death or hospitalisation at Day 28 by 5.15% in those treated within 5 days. The effect was lowest in participants who were SARS CoV2 antibody positive at baseline (1.34% compared with 10.25% in those who were antibody negative).
- The feasibility of nirmatrelvir+RTV use may be limited by the requirement that treatment needs to be initiated within 5 days of symptom onset. In addition, access to more affordable generic products will be restricted to the public sector.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation		x			

Recommendation: The Committee suggests that nirmatrelvir+RTV not be used for the treatment of COVID-19.
Rationale: Although there is evidence from a single RCT that nirmatrelvir+RTV reduces the risk of hospitalisation and death in adults with mild to moderate COVID-19 who are at high-risk for progression to severe COVID-19, and is well tolerated, its use requires rapid access to definitive diagnosis and initiation within 5 days of the onset of symptoms. Use of nirmatrelvir+RTV is contraindicated in pregnancy, so women of childbearing potential need to take effective contraception. Ritonavir increases the concentration of nirmatrelvir by slowing its breakdown through the cytochrome P450 pathway. This results in many potential drug-drug interactions. The efficacy and safety of nirmatrelvir+RTV has not been studied in patients previously vaccinated against COVID-19. Products containing nirmatrelvir and ritonavir (as co-packaged, separate oral solid dosage form) have yet to be registered in South Africa. The review will be updated when there is more information on the availability and pricing of generic products.
Level of Evidence: Moderate certainty evidence.
Review indicator: Registration of generic and/or innovator brands in South Africa, or access via section 21, with declared prices.

(Refer to appendix 1 for the evidence to decision framework)

NEML MAC for COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

The U.S. Food and Drug Administration issued an emergency use authorization (EUA) for nirmatrelvir+RTV tablets for the treatment of mild-to-moderate coronavirus disease (COVID-19) in December 2021. The EUA allows use of nirmatrelvir+RTV in patients 12 years of age and older, weighing ≥40 kilograms, with laboratory-confirmed SARS-CoV-2 infection, at high risk for progression to severe disease, specifically hospitalisation or death. [1]

Nirmatrelvir works by inhibiting M^{pro}, a viral enzyme critical to SARS-CoV-2 replication. Ritonavir increases the concentration of nirmatrelvir by slowing its breakdown through the cytochrome P450 pathway. This results in many potential drug-drug interactions.[2]

The European Medicines Agency (EMA) currently recommends that nirmatrelvir+RTV be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. They further recommend that it not be used with other medicines where a drug-drug interaction is predicted and that it not be used during pregnancy and in people who can become pregnant and who are not using contraception.[3]

RESEARCH QUESTION: Should nirmatrelvir+RTV be used to treat confirmed COVID-19?

METHODS

This evidence summary reflects data from a single peer-reviewed publication (Hammond et al., 2022)[4] as well as data provided by the EMA (European Medicines Agency. EMA, 2021). The published data reflected the full analysis of the phase 2/3 C4671005 clinical trial. The EMA document summarised relevant pre-clinical and earlier phase clinical trial data, as well as the interim and full analyses of C4671005. The main characteristics and trial outcomes are shown in Table 1.

Risk of bias for the trial was assessed independently and in duplicate by two reviewers (NB and NG) using the ROB 2.0 tool). We calculated risk ratios and 95% confidence intervals for the pre-specified outcomes, using an intention to treat approach. Table 3 is a GRADE Summary of Findings table for the comparison nirmatrelvir+RTV compared to usual care. [5]

Eligibility criteria for review

Population: Patients with confirmed SARS-CoV-2 infection; no restriction to age or co-morbidity

Intervention: Nirmatrelvir+RTV, either alone or in combination with other medicines

Comparators: Standard of care or placebo

Outcomes: Mortality; progression to hospitalisation; duration of hospitalisation; progression to requiring oxygen; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement; adverse reactions and adverse events

Study designs: Systematic reviews of randomised controlled trials; individual randomised controlled trials

RESULTS

Results of search

We did not conduct a formal search for this evidence summary. A peer reviewed publication (Hammond et al., 2022)[4] and the data submitted by European Medicines Agency (EMA) (16 December 2022) (European Medicines Agency. EMA, 2021)[3] were retrieved, reviewed and summarised. The main characteristics and outcomes from the phase 2/3 C4671005 clinical trial are shown in Table 2.

Description of the trial

The EPIC-HR trial investigated the effectiveness of nirmatrelvir+RTV compared to standard of care, in the management of COVID-19. In a 1:1 ratio, 500 mg of nirmatrelvir plus 100 mg of ritonavir, or placebo, were administered orally every 12 hours for 5 days to symptomatic, unvaccinated, non-hospitalised adults at risk for severe COVID-19. Participants were recruited from the United States (105 sites), Bulgaria (30 sites), South Africa, (28 sites), Brazil (26 sites), India (19 sites), Mexico (18 sites), Ukraine (17 sites), Turkey (16 sites), Japan (10 sites), Spain (10 sites), Russia (9 sites), Argentina (8 sites), Colombia (8 sites), Poland (7 sites), South Korea (7 sites), Hungary (6 sites), Taiwan (5 sites), Malaysia (4 sites), Czech Republic (4 sites), Thailand (3 sites) and Puerto Rico (3 sites).

A total of 2246 patients underwent randomisation, where 1120 received nirmatrelvir+RTV and 1126 received placebo. Of 2246 participants randomised, 2102 had completed safety follow-up at day 34 and none had yet completed longer follow up through week 24.

The investigators reported results for two treatment groups: those treated within 5 days of onset of symptoms (n=1039 and n=1046 in the nirmatrelvir+RTV and placebo groups, respectively); and those treated within 3 days of onset of symptoms (modified ITT) (n=697 and n=682 in the nirmatrelvir+RTV and placebo groups, respectively).

The main exclusion criteria included having a history of previous confirmed SARS-CoV2 infection or previous hospitalisation for the medical treatment of COVID-19; having current need for hospitalisation or anticipated need for hospitalisation within 48 hours after randomisation;; having received or expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit and having an oxygen saturation of <92%. (Table 1 summarises the characteristics and results reported of the included trial). The trial describes two interim analyses. The first interim analysis was conducted after 45% of participants had completed day 28 assessments in the mITT analysis set (i.e., 28 days after randomisation). The second interim analysis was conducted when 70% participants completed day 28 assessments.

Appraisal RoB 2.0

Overall, the trial was well reported. Sequence generation and allocation concealment were well managed, blinding was applied to participants, researchers and outcome assessors, minimising the likelihood of detection of performance bias. The concern was regarding reporting results of sub-sets of the overall population, thereby reporting sub-group that may not have been adequately powered to answer the question and because of selection of those that could be identified by 3 days, may introduce selection bias. The analysis plan was pre-specified in the protocol. Overall, risk of bias was assessed as having serious 'bias due to missing outcome data' (Table 2).

Effects of the intervention

The following outcomes were not reported in the trial report: Progression to requiring oxygen; duration of hospitalisation; progression to ICU admission; duration of ICU stay; duration of mechanical ventilation; clinical improvement on an ordinal scale at chosen time points, and time to clinical improvement. The manuscript reported a composite outcome of death or hospitalisation as follows:

Modified intention to treat analysis (1379 of the 2246 patients in the full analysis population who commenced treatment within 3 days after symptom onset and did not receive monoclonal antibodies):

Covid-19–related hospitalisation or death from any cause at 28 days were 0.72% and 6.45% in the nirmatrelvir and placebo groups, respectively, corresponding to a difference of −5.81 percentage points (95% CI, –7.78 to –3.84; P<0.001) and an 88.9% relative risk reduction in Covid-19–related hospitalisation or death from any cause.
For our report we extracted results for the outcomes all-cause mortality or hospitalisation; adverse effects and serious adverse effects.

1. All-cause mortality

Treated within 3 days of symptom onset: no deaths (0/697; 0%) compared to 9/682 (1.32%) in the active and placebo groups (RR 0.05; 95% CI 0.00 - 0.88; low certainty evidence).

Treated within 5 days of symptom onset: 0/1120 deaths (0%) compared to 12/1126 (1.07%) in the placebo group (RR 0.04; 95% CI 0.00 - 0.68; moderate certainty evidence). The calculated fragility index for mortality (started within 5 days) is 4.

2. Hospitalisation

Treated within 3 days of symptom onset: there were 5/697 (0.72%) compared to 44/682 (6.45%) hospitalisations in the active and placebo groups (RR 0.11; 95% CI 0.04 - 0.28; moderate certainty evidence).

Treated within 5 days of symptom onset: there were 8 /1120 hospitalisations (0.71%) compared to 65/1126 (5.77%) in the placebo group (RR 0.12; 95% CI 0.06 - 0.26; high certainty evidence).

3. Adverse events

Overall, there were 476/1109 (42.92%) adverse events in the nirmatrelvir+RTV group compared to 525/1115 (47.09%) in the safety analysis population (received at least one dose of trial medicine) - RR 0.91 (95% CI 0.83, 1.00) (moderate certainty).

In terms of adverse events considered related to the medicine or placebo, there were 123/1109 (11.09%) in the active group compared to 52/1115 (4.66%) in the placebo group - RR 2.38 (95% CI 1.74, 3.25) (moderate certainty). Adverse events considered by the site investigator to be related to the trial drug or placebo were more common among recipients of nirmatrelvir+RTV (86/1109 participants, 7.8%) than among placebo recipients (42/1115 participants, 3.8%). Adverse events experienced by those participants included dysgeusia (5.6% with nirmatrelvir+RTV vs 0.3% with placebo), diarrhoea (3.1% vs 1.6%) and vomiting (1.1% vs 0.8%).

4. Serious adverse events

Overall, fewer serious adverse events (18/1109 (1.6%) vs. 74/1115 (6.6%); RR 0.24; 95% CI 0.15, 0.41; high certainty) and fewer adverse events leading to discontinuation of the drug or placebo (23 (2.1%) vs. 47 (4.2%)) occurred in the active group. Adverse events and serious AEs are summarised below in the Table from the manuscript (Table 1).

Table 1. Adverse events reported in the manuscript Hammond J et al; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542. Epub ahead of print. PMID: 35172054.

Table 2. **Summary of Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation through Day 34 (Safety Analysis Population).***

Adverse Event Category	Nirmatrelvir plus Ritonavir (N=1109)	Placebo (N=1115)
Events that emerged during treatment period		
No. of adverse events	476	525
Patients with adverse events — no. (%)		
Any adverse event	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13† (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)
Events considered to be related to drug or placebo		
No. of adverse events	123	52
Patients with adverse events — no. (%)		
Any adverse event	86 (7.8)	42 (3.8)
Serious adverse event	1 (<0.1)	0
Maximum grade 3 or 4 adverse event	5 (0.5)	5 (0.4)
Maximum grade 5 adverse event	0	0
Discontinued drug or placebo because of adverse event	9 (0.8)	7 (0.6)
Had dose reduction or temporary discontinuation owing to adverse event	2 (0.2)	3 (0.3)

* Shown are data for all patients who received at least one dose of drug or placebo.
† All reported deaths were related to Covid-19; causes of death included Covid-19 pneumonia (8 patients), Covid-19 (3 patients), pneumonitis (1 patient), and acute respiratory failure (1 patient).

CONCLUSION

One well-conducted RCT showed that treatment with nirmatrelvir+RTV early in COVID-19 (within 5 days of symptom onset) probably reduces hospitalisation and death in unvaccinated, non-hospitalised adults at high risk of progression to severe COVID-19. Nirmatrelvir+RTV efficacy and safety in patients who have previously received a COVID-19 vaccine is unknown, and important key populations were excluded from the study, including children, adolescents, pregnant women and people living with HIV with HIV viral loads >400 copies/mL. In addition, there are important logistic difficulties that would have to be overcome for the treatment to be rolled out successfully in South Africa, including timeous diagnosis of COVID-19, access to a prescription and to the dispensed product, the exclusion of patients who might be expected to have significant drug-drug interactions, and appropriate selection of high-risk individuals at primary health care level.

Reviewers: Gary Reubenson, Jeremy Nel, Renee de Waal, Tamara Kredo, Ntombifuthi Blose, Natasha Gloeck (risk of bias assessment), Milli Reddy, Trudy Leong.

Declaration of interests: GR (Department of Paediatrics & Child Health, University of the Witwatersrand); JN (Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand); Renee De Waal (Centre for Infectious Disease Epidemiology and Research, University of Cape Town); MR (Better Health Program) and TL (Essential Drugs Programme, National Department of Health) have no interests pertaining to nirmatrelvir+RTV. TK (Cochrane South Africa, South African Medical Research Council (SAMRC); Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network and TK, NB, NG are partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.

Table 1: Characteristics of included study

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias (ROB 2.0)
European Medicines Agency. EMA. Conditions of Use, Conditions for Distribution and Patients Targeted. 2021. Hammond J et al; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542. Epub ahead of print. PMID: 35172054.	*Design:* Phase 2/3 randomised, double-blind, placebo-controlled Multinational	Non-hospitalised, symptomatic, unvaccinated adult participants with COVID-19 at increased risk of progressing to severe illness ***Sample size*:** N = 2246. (Full Analysis) age: 46 years; 1148 patients (51.1%) were male, 1607 (71.5%) were White & 315 (14.0%) Asian. ***Main inclusion criteria:*** • Confirmed SARS-CoV-2 infections determined by RT-PCR (other molecular or antigen tests) within 5 days prior to randomization • Initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to randomization • ≥1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically related technological dependence, or were 60 years of age and older regardless of comorbidities ***Main exclusion criteria:*** • History of hospitalization for treatment of COVID-19 • Current need or anticipated need for hospitalization within 48 hours after randomization	300 mg of nirmatrelvir plus 100 mg of ritonavir 12 hourly for 5 days (10 doses total), vs placebo in a 1:1 ratio. ***Control:*** Placebo "Company selected placebo as comparator since there were no-globally approved Standard of Care (SoC) treatment for this patient population as of June 2021".	Efficacy assessments through Day 28, a safety follow-up period through Day 34, and long-term follow-up at Weeks 12 and 24. **Primary outcome:** Proportion with COVID-19 related hospitalisation or death from any cause Day 28 **Results: primary outcomes:** *nirmatrelvir+ritonavir vs placebo:* **COVID-19–related hospitalization or death by day 28** • **Modified intention- to treat population:** 3/389 [0.77%]; 0 deaths) vs 27/385 [7.01%]; 7 deaths), significant difference of −6.32 % points (95% CI, –9.04 to –3.59; P<0.001). Relative risk reduction: 89.1% • ***mITT-1:*** 5.765% (95% CI: -7.917% to - 3.613%; p<0.0001) absolute reduction, from 6.764% to 0.999%. • **Treated within 3 days of symptom onset:** (1379/2246 patients in the full analysis), 5/697 (0.72%) vs 44/ 682 (6.45%) difference of −5.81 % points (95% CI, –7.78 to –3.84; P<0.001). 88.9% relative risk. 0 vs 9 deaths • **Treatment within 5 days after symptom onset (mITT):** 8/1039 (0.77%) vs 66/1046 (6.31%) patients (P<0.001). Relative risk reduction: 87.80%. • **Treatment within 5 days after symptom onset (ITT):** 8/1120 (0.71%) vs 66/1126 (5.86%) patients. Relative risk reduction: 87.81% ***Secondary outcomes:*** • Incidence of treatment emergent adverse events • Incidence of SAEs & AE leading to discontinuations *nirmatrelvir+ritonavir vs placebo:* • ***Any AEs:*** 22.6% vs 23.9% • **Most frequently reported AE & event considered to be related to drug or placebo**: ○ dysgeusia (5.6%, vs 0.3%) ○ diarrhea (3.1% vs. 1.6%), ○ fibrin D-dimer increase (1.9% vs. 2.8%), ○ alanine aminotransferase increase (1.5% vs. 2.4%), ○ headache (1.4% vs. 1.3%), ○ creatinine renal clearance decrease (1.4% vs. 1.6%), ○ nausea (1.4% vs. 1.7%), ○ vomiting (1.1% vs. 0.8%);	**Overall judgement with regards to risk of bias: SERIOUS** ***Randomisation:*** Was conducted **LOW RISK** but concern raised in reporting of results in sub-sets of the overall population, potentially undermining the purpose of randomization and introducing ***Selection Bias:*** 1) sub-groups – underpowered to answer question as posed by the trial; 2) when reporting sub-set, with selection of a specific population, not specifically determined by randomization, but rather by those who managed to be identified at 3 days – no certainty that randomization was sufficient, and there is therefore the element of selection bias: **HIGH RISK** ***Measurement of the outcome:*** Missing outcome data: **HIGH RISK** ***Detection or performance bias:*** Sequence generation & allocation concealment were well managed, blinding was applied to participants, researchers & outcome assessors. Analysis plan noted as pre-specified in protocol. Overall, trial was well reported referring

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias (ROB 2.0)
		• Prior to current disease episode, any confirmed SARS-CoV-2 infection • Has or expected to receive any dose of a SARS-CoV-2 vaccine before the Day 34 visit. • Oxygen saturation <92%		AEs were nonserious, mostly grade 1 or 2, & resolved • **SAEs (occurring in ≥2 patients): 1.6% vs 6.6%** • Covid-19 pneumonia (6 [0.5%], vs 37 [3.3%]), • 0 vs 13 deaths among placebo recipients, all COVID-19–related (COVID-19 pneumonia, n=8; COVID-19, n=3; pneumonitis, n=1; & acute respiratory failure, n=1) **AEs that led to discontinuation of the trial drug or placebo in >1 patient** 2.1% vs 4.2% were Covid-19 pneumonia, nausea, decreased renal creatinine clearance, vomiting, COVID-19, decreased glomerular filtration rate, pneumonia, pneumonitis, decreased white-cell count, & dysgeusia.	to the publication and EMA report.: **LOW RISK**

Table 2. Characteristics of planned and ongoing studies

Treatment (per arm)	n	Severity at enrollment	Sponsor/ Funder	Registry number	url link
(1) PF-07321332 + ritonavir vs (2) Placebo [EPIC-HR]	2260	Mild	Pfizer	NCT04960202	https://clinicaltrials.gov/show/NCT04960202
(1) Pf-07321332 vs (2) Ritonavir vs (3) Placebo	2634	Close contacts to covid patients	Pfizer Inc.	EUCTR2021-002894-24-ES	https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002894-24/ES
(1) Pf-07321332 + ritonavir vs (2) Placebo [EPIC-SR]	1140	Mild	Pfizer	NCT05011513	https://clinicaltrials.gov/show/NCT05011513
(1) Pf-07321332 + ritonavir vs (2) Pf-07321332 + ritonavir vs (3) Placebo	2 634	Close contacts to covid patients	Pfizer	NCT05047601	https://clinicaltrials.gov/show/NCT05047601

Table 3: Summary of findings

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirmatrelvir + Ritonavir	placebo or SoC	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality - Treated less than 3 Days after Onset of Symptoms											
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/697 (0.0%)	9/682 (1.3%)	**RR 0.05** (0.00 to 0.88)	**13 fewer per 1,000** (from 2 fewer to --)	⊕⊕◯◯ Low
All-cause mortality - Treated within 5 Days after Onset of Symptoms											
1	randomised trials	not serious	not serious	not serious	serious[b]	none	0/1120 (0.0%)	12/1126 (1.1%)	**RR 0.04** (0.00 to 0.68)	**10 fewer per 1,000** (from 3 fewer to --)	⊕⊕⊕◯ Moderate
Hospitalisation - < 3 days											
1	randomised trials	serious[a]	not serious	not serious	not serious	none	5/697 (0.7%)	44/682 (6.5%)	**RR 0.11** (0.04 to 0.28)	**57 fewer per 1,000** (from 62 fewer to 46 fewer)	⊕⊕⊕◯ Moderate
Hospitalisation - <5 days											
1	randomised trials	not serious	not serious	not serious	not serious	none	8/1120 (0.7%)	65/1126 (5.8%)	**RR 0.12** (0.06 to 0.26)	**51 fewer per 1,000** (from 54 fewer to 43 fewer)	⊕⊕⊕⊕ High
Serious adverse events											
1	randomised trials	not serious	not serious	not serious	not serious	none	18/1109 (1.6%)	74/1115 (6.6%)	**RR 0.24** (0.15 to 0.41)	**50 fewer per 1,000** (from 56 fewer to 39 fewer)	⊕⊕⊕⊕ High
Adverse events											
1	randomised trials	serious[a]	not serious	not serious	not serious	none	476/1109 (42.9%)	525/1115 (47.1%)	**RR 0.91** (0.83 to 1.00)	**42 fewer per 1,000** (from 80 fewer to 0 fewer)	⊕⊕⊕◯ Moderate

CI: confidence interval; **RR:** risk ratio

Explanations

a. Downgraded by 1 level for risk of bias: this is an interim analysis, and the trial results are reporting on sub-set of population.

b. Downgraded by 1 level for imprecision: low numbers of events and wide confidence interval

Appendix 1: Evidence to decision framework

Desirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate **x Large** ○ Varies ○ Don't know	**Nirmatrelvir+RTV compared to placebo or SoC for COVID-19 management**	Benefit likely to be significantly less in those with previous infection (% reduction in primary endpoint in those with baseline SARS CoV-2 serology positive was only 1.34% vs 10.25% in those whose serology was negative). Benefit likely to be significantly less in those with previous vaccination. Benefit unknown for key patient populations that were excluded, including pregnant women and HIV patients with HIV viral loads >400 copies/mL. Benefits potentially lower if infection caused by variant with inherently lower risk of causing severe disease.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or SoC	**Risk with Nirmatrelvir+RTV**			
All-cause mortality - < 3 days of onset of symptoms	13 per 1,000	**1 per 1,000** (0 to 12)	**RR 0.05** (0.00 to 0.88)	1379 (1 RCT)	⊕⊕◯◯ Low[a,b]
All-cause mortality - < 5 days of onset of symptoms	11 per 1,000	**0 per 1,000** (0 to 7)	**RR 0.04** (0.00 to 0.68)	2246 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Hospitalisation - < 3 days	65 per 1,000	**7 per 1,000** (3 to 18)	**RR 0.11** (0.04 to 0.28)	1379 (1 RCT)	⊕⊕⊕◯ Moderate[a]
Hospitalisation - <5 days	58 per 1,000	**7 per 1,000** (3 to 15)	**RR 0.12** (0.06 to 0.26)	2246 (1 RCT)	⊕⊕⊕⊕ High
Serious adverse events	66 per 1,000	**16 per 1,000** (10 to 27)	**RR 0.24** (0.15 to 0.41)	2224 (1 RCT)	⊕⊕⊕⊕ High
Adverse events	471 per 1,000	**428 per 1,000** (391 to 471)	**RR 0.91** (0.83 to 1.00)	2224 (1 RCT)	⊕⊕⊕◯ Moderate[a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

a. Downgraded by 1 level for risk of bias: this is an interim analysis, and the trial results are reporting on sub-set of population.
b. Downgraded by 1 level for imprecision: low numbers of events and wide confidence interval

Undesirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate **x Small** ○ Trivial ○ Varies ○ Don't know	See Summary of findings table above.	Drug side-effects largely consisted of GIT side-effects. Overall rates of SAEs were *lower* in the active arm compared to placebo.

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low **X Moderate** ○ High ○ No included studies	Low certainty of evidence for mortality.	Single RCT. Low absolute numbers of deaths.
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X Probably no important uncertainty or variability** ○ No important uncertainty or variability	No survey data.	There is a lack of research evidence from stakeholders. Although a survival benefit is likely to be valued, reduced hospitalisation is also likely to be highly desirable when health systems are under pressure. Concern has been expressed that prescribers would refuse to restrict use to those with increased risk, but would feel ethically compelled to treat all identified patients.
Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison **x Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The committee judged that balance of effects probably favours nirmatrelvir+RTV compared to standard of care in unvaccinated adults suspected of being at high risk for severe disease with confirmed Covid-19 treated within 5 days of symptoms starting.	Benefits are substantial, undesirable effects are minor.
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies **x Don't know**		Cost unknown for local use and not SAHPRA registered. Uncertainty regarding generic licensing of nirmatrelvir $US 530 per treatment course

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies **X No included studies**	No included studies.	Local cost unknown currently.
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced equity **X Probably reduced** ○ Probably no impact ○ x Probably increased ○ Increased equity ○ Varies ○ Don't know	It is unclear when a product will be registered in South Africa and at what price. The affordability of the product could impact equity.	Medicine may have different availability and/or costs in private vs public sectors.
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies **X Don't know**	No research evidence is available.	
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No **X Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	No products have yet been registered in South Africa (innovator nor generic formulations).	Access to a SAHPRA-approved generic formulation is not currently available. Cost of treatment is unknown and global supply is already limited by the number of units that be manufactured and sold already. Requires a patient to test for COVID, get the result and get the medication within 5 days from symptom onset. The indication would be for confirmed COVID-19 by rapid or PCR, and not purely PCR confirmed. Requires moderately complex selection of patients to ensure the medicine is only given to those at high risk of severe

		COVID-19 disease. Use of the medicine would require patient education. Important drug-drug interactions – would need to screen for concomitant drugs that are strong CYP3A4 inducers or inhibitors. Drug interactions with protease inhibitors and also diabetic and epileptic drugs; these constitute high risk COVID-19 patients.

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	14 March 2022	GR, JN, RdW, TK, NB, NG, MR, TL	Nirmatrelvir+RTV not be used for the treatment of COVID-19. Single RCT shows reduction in hospitalisation and death in adults with mild to moderate COVID-19, at high-risk for progression to severe COVID-19. However, rapid access and initiation within 5 days of onset of symptoms by patients with confirmed COVID-19. Use of nirmatrelvir+RTV is contraindicated in pregnancy, so women of childbearing potential need to take effective contraception. There is a potential of many drug-drug interactions. Not been studied in patients previously vaccinated against COVID-19. Products have yet to be registered in South Africa. Review will be updated when there is more information on availability and pricing of generic products.
2.0	14 March 2022	GR, JN, RdW, TK, NB, NG, MR, TL	Editorial amendment.
3.0	14 March 2022	GR, JN, RdW, TK, NB, NG, MR, TL	Error amended from, "The absolute risk reduction (ARR) of 1.07% (95% CI 0.47 to 0.67%)" to "The absolute risk reduction (ARR) of 1.07% (95% CI 0.47 to 1.67%)".

For internal NDoH use:
WHO INN: nirmatrelvir: not available as yet; ritonavir
ATC: nirmatrelvir: not available as yet; ritonavir: J05AE03
ICD10: U07.1/U07.2

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[4] Hammond J et al; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542.
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