Nirmatrelvir/Ritonavir

Section last reviewed and updated 4/12/23

Last literature search conducted 3/31/23

Resources:

- **University of Liverpool:** COVID-19 drug interaction checker
- **University of Liverpool:** HIV drug interaction checker

Recommendation 1: In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests nirmatrelvir/ritonavir initiated within five days of symptom onset rather than no nirmatrelvir/ritonavir. (Conditional recommendation†, Low certainty of evidence)

Remarks:

- Patients' medications need to be screened for serious drug interactions
- Dosing based on renal function:
    - Estimated glomerular filtration rate (eGFR) > 60 ml/min: 300 mg nirmatrelvir/100 ritonavir every 12 hours for five days
    - eGFR ≤60 mL/min and ≥30 mL/min: 150 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
    - eGFR <30 mL/min: not recommended
- Patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital may also receive nirmatrelvir/ritonavir

**Options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, remdesivir for a 3-day course, molnupiravir, and neutralizing monoclonal antibodies. Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.*

†*The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.*

Figure 1. FDA EUA criteria for the use of nirmatrelvir/ritonavir co-packaged as Paxlovid™ [1]

Paxlovid is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.

Why is nirmatrelvir/ritonavir considered for treatment?

Nirmatrelvir is an inhibitor to the main protease (Mpro) of SARS-CoV-2; inhibition of this enzyme blocks viral replication. Nirmatrelvir is a substrate of the cytochrome P450 3A4 isoenzyme system and is co-packaged with an HIV-1 protease inhibitor, ritonavir, a potent inhibitor of cytochrome P450 3A4. Coadministration results in higher concentrations and a longer half-life of nirmatrelvir, allowing for every-12-hour dosing. The FDA granted EUA to nirmatrelvir/ritonavir on December 22, 2021 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (≥12 years of age and weighing ≥40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death [1].

Summary of the evidence

Our search identified one RCT reporting on treatment of mild-to-moderate COVID-19 in patients at high risk for progression to severe disease [1]. In addition, the search identified one RCT reporting on treatment of mild-to-moderate COVID-19 in 264 hospitalized patients [2]. Some data used to prepare this recommendation were extracted from the FDA EUA document.

Benefits

Nirmatrelvir/ritonavir

All-cause mortality through day 28 may be lower in ambulatory patients receiving nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir (RR: 0.04; 95% CI: 0.00, 0.69; low CoE). Patients treated with nirmatrelvir/ritonavir rather than no nirmatrelvir/ritonavir may have fewer COVID-19-related hospitalizations (RR: 0.12; 95% CI: 0.06, 0.26; low CoE). The composite endpoint of COVID-19-related hospitalizations or mortality was lower in patients receiving nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir (RR: 0.12; 95% CI: 0.06, 0.25; low CoE).

In hospitalized patients receiving nirmatrelvir/ritonavir, all-cause mortality may be lower (RR: 0.63; 95% CI: 0.21, 1.86; low CoE); however, no benefit has been shown for need for invasive mechanical ventilation or length of hospital stay (RR: 1.67; 95% CI: 0.62, 4.45; low CoE and MD -0.38 days; 95% CI: -2.09, 1.32; low CoE, respectively.

Harms

Nirmatrelvir/ritonavir

Limited evidence from hospitalized patients with mild-to-moderate COVID-19 receiving nirmatrelvir/ritonavir suggest increased serious adverse events and adverse events (RR 1.20; 95% CI: 0.38, 3.84; low CoE and RR: 1.40; 95% CI: 0.65, 3.04; low CoE).

Serious treatment-emergent adverse events were not reported in the FDA EUA.

Given co-formulation with ritonavir as a pharmacokinetic booster, there is potential for significant drug interactions. Contraindications exist between agents that can have their levels increased or decreased by nirmatrelvir and/or ritonavir and agents that can increase the metabolism of the components of nirmatrelvir and/or ritonavir, resulting in a loss of virologic response and possible resistance. These drug interactions can result in treatment failure or serious adverse events, which may lead to severe, life-threatening, or fatal events from greater exposures (i.e., higher levels) of concomitant medications. See **Figures 2 and 3**.

Figure 2. Nirmatrelvir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions [1.] *

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvaptan

*Please check drug interactions before initiating nirmatrelvir/ritonavir as the table above does not list all therapeutic agents or classes with potential interactions; see **Liverpool COVID-19 interactions website**.

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 2 April 2023.

Figure 3. Nirmatrelvir/ritonavir is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance [1]

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Antimycobacterials: rifampin • Herbal products: St. John's Wort (hypericum perforatum)

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 26 April 2023.

Less severe but clinically meaningful drug interactions may also occur when nirmatrelvir/ritonavir is co-administered with other agents. Levels of immunosuppressive agents such as tacrolimus, cyclosporine, or sirolimus can be increased when administered with nirmatrelvir/ritonavir. Hormonal contraceptives containing ethinyl estradiol may possibly have reduced effectiveness due to lowered ethinyl estradiol levels when administered with nirmatrelvir/ritonavir. Women of childbearing potential should be counseled to use a back-up, non-hormonal method of contraception.

Patients with moderate renal impairment (eGFR <60 and ≥30 mL/min) must be counseled that they will only take one 150-mg nirmatrelvir tablet (oval shape, pink) with one 100-mg tablet of ritonavir twice daily, instead of the regular dose of two 150-mg nirmatrelvir (300 mg) tablets with one 100-mg tablet of ritonavir twice daily. Pharmacists need to adhere to the specific instructions when dispensing the product according to instructions provided in the EUA [3]. Given the lack of renal function/eGFR data at the point of dispensing, providers must specify the numeric dosage of each agent on the prescription to ensure the correct dose is provided to the patient at the point of dispensing. There are no data in patients with severe renal disease (eGFR ≤ 30 mL/min); this medication is currently not recommended in patients with severe renal disease until more data on dosing in this population are available.

There are no dose adjustments needed for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, however, data are lacking in patients with Child-Pugh C, and nirmatrelvir/ritonavir is therefore not recommended in this population.

According to the EUA, nirmatrelvir/ritonavir use may be associated with a risk of developing HIV resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Other considerations

<u>Nirmatrelvir/ritonavir</u>

The panel agreed that the overall certainty of the evidence for the treatment of ambulatory patients was low; there are concerns with the inability to exclude potential risks to

bias because of limited availability of study details within the EUA, and there is imprecision due to a low number of events reported. The EUA did not report safety data (e.g., adverse events or severe adverse events) from the trial. The panel agreed that the benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk of severe disease; however, recognized concerns with drug interactions must be considered.

The evidence confirms that using nirmatrelvir/ritonavir early in the disease process when viral loads are high confers maximum benefit. It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course. Observational studies have shown a similar benefit among vaccinated patients infected with newer variants. The panel recognized the need for additional evidence to inform decisions regarding treatment of hospitalized patients with COVID-19.

Viral rebound in patients treated with nirmatrelvir/ritonavir

Recurrence of symptoms associated with viral rebound has been estimated to occur in nirmatrelvir/ritonavir treated patients in 0.8% to 6.6% in various trials, including the EPIC HR trial [4, 5]. Rebound has also been described with molnupiravir (5.8% [6] and no antiviral treatment [4, 7]). Observational evidence suggests hospitalization after nirmatrelvir/ritonavir treatment to be infrequent, ranging from 0.11% to 0.44% [8, 9]. No direct evidence was found on the effect of repeat nirmatrelvir/ritonavir treatment (on any other direct acting antivirals) in patients experiencing symptomatic viral rebound after initial antiviral treatment. The effect of repeating the same drug (for another course) after a viral rebound is unknown regards to patient important outcomes such as need for hospitalization, invasive ventilation, or death. Study limitations of observational medical records database studies includes misclassifications in admission diagnosis and absence of adequate compliance determination, among others.

Conclusions and research needs for this recommendation

<u>Nirmatrelvir/ritonavir</u>

The guideline panel suggests the use of nirmatrelvir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who are within

five days of symptom onset. More data are needed on the potential adverse effects of this medication. In addition, future studies are important to inform the impact of nirmatrelvir/ritonavir in hospitalized patients, in vaccinated high-risk patients with mild-to-moderate COVID-19 and in symptomatic immune- compromised patients with persistently elevated viral loads.

Table 1. GRADE evidence profile, Recommendation 1

Question: Nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

Last reviewed and updated 2/3/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nirmatrelvir/ ritonavir	no nirmatrelvir/ ritonavir	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 28 days)												
1[1]	randomized trials	serious [a]	not serious	not serious [b]	serious [c]	none	0/1039 (0.0%)	12/1046 (1.1%)	**RR 0.04** (0.00 to 0.68)	**11 fewer per 1,000** (from 18 fewer to 5 fewer) [d]	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related hospitalizations (follow-up: 28 days)												
1[1]	randomized trials	serious [a]	not serious	not serious [b,e]	serious [c]	none	8/1039 (0.8%)	65/1046 (6.2%)	**RR 0.12** (0.06 to 0.26)	**55 fewer per 1,000** (from 58 fewer to 46 fewer)	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related hospitalization or all-cause death (follow-up: 28 days)												
1[1]	randomized trials	serious [a]	not serious	not serious [b]	serious [c]	none	8/1039 (0.8%)	66/1046 (6.3%)	**RR 0.12** (0.06 to 0.25)	**56 fewer per 1,000** (from 59 fewer to 47 fewer)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings are derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Evidence profile based on information reported in FDA EUA and due to limited available study details, unable to exclude potential risks of bias. Concerns about selective outcome reporting as hospitalization or death from any cause and all-cause mortality are reported out of 10 outcome measures identified in the trial protocol, including serious adverse events and adverse events.
b. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I.
c. Small number of events; fragility present
d. Recalculated due to zero events in the intervention arm.
e. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™. Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.

Table 2. GRADE evidence profile, Recommendation 1 Remark

Question: Nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir for hospitalized patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

Last reviewed and updated 4/12/2023

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nirmatrelvir /ritonavir	no nirmatrelvir/ritonavir	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 28 days)												
1[1]	randomized trials	not serious [a]	not serious	not serious	very serious [b,c]	none	5/132 (3.8%)	8/132 (6.1%)	**RR 0.63** (0.21 to 1.86)	**22 fewer per 1,000** (from 48 fewer to 52 more)	⨁⨁◯◯ LOW	CRITICAL
Invasive mechanical ventilation (follow-up: 28 days)												
1[1]	randomized trials	not serious [a]	not serious	not serious	very serious [b,d]	none	10/132 (7.6%)	6/132 (4.5%)	**RR 1.67** (0.62 to 4.45)	**30 more per 1,000** (from 17 fewer to 157 more)	⨁⨁◯◯ LOW	CRITICAL
Length of hospitalization (follow-up: 28 days)												
1[1]	randomized trials	not serious [a]	not serious	not serious	very serious [b,d]	none	132	132	-	MD **0.38 lower** (2.09 lower to 1.32 higher)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events												
1[1]	randomized trials	not serious [a]	not serious	not serious	very serious [b,e]	none	6/132 (4.5%)	5/132 (3.8%)	**RR 1.20** (0.38 to 3.84)	**8 more per 1,000** (from 23 fewer to 108 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nirmatrelvir /ritonavir	no nirmatrelvir/ritonavir	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomized trials	not serious [a]	not serious	not serious	very serious [b,e]	none	14/132 (10.6%)	10/132 (7.6%)	**RR 1.40** (0.65 to 3.04)	**30 more per 1,000** (from 27 fewer to 155 more)	⨁⨁◯◯ LOW	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings are derived from evidence that has not been peer reviewed or published.

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Participants were aware of treatment assignment (open label); however, treating physicians remained blinded to the treatment group.
b. Few events do not meet the optimal information size and suggest fragility in the estimate.
c. The 95% CI may not include a clinically meaningful effect.
d. The 95% CI cannot exclude the potential for benefit or harm.
e. The 95% CI cannot exclude no harm.

References

1. Liu J, Pan X, Zhang S, et al. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac **2023**; 33: 100694.

Table 3. GRADE evidence profile, viral rebound

Question: Nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who have experienced viral rebound after completion of initial course of nirmatrelvir/ritonavir

Last reviewed and updated 3/3/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nirmatrelvir/ritonavir	no nirmatrelvir/ritonavir	Relative (95% CI)	Absolute (95% CI)		
Hospitalizations or all-cause deaths												
4[1-4]	observational studies [a]	serious [b]	not serious	not serious	not serious	none	• No direct evidence was found investigating the effect of repeat nirmatrelvir/r (n/r) treatment in patients experiencing symptomatic viral rebound after initial antiviral treatment • 7 day rates of viral rebound after n/r treatment has been estimated to be in the range of 2.3% (17/980) in the registration trial EPIC-HR to 3.5% (392/11,270); and seen in data from Hongkong (Wong 2023: 6.6.% (16/242) • Comparative rates of viral rebound have been seen in untreated persons (1.7%; 17/980); and data from Hongkong (Wong 2023: 4.5.% (170/3787). • Molnupiravir rebound has been reported to occur in 5.9% (139/2,374); and seen in data from Hongkong (Wong 2023: 4.8.% (27/563) • Observational evidence showed hospitalization after n/r has been infrequent ranging from 0.11% (6/5,287) to 0.4% (2/483) and 0.44% (50/11,270) for n/r; and 0.84% for molnupiravir (Malden 2022, Ranagath 2022) • 2 deaths out of 6 patients occurred in those hospitalized in one study • The effect of repeating the same drug (for another course) after a viral rebound is unknown for patient important outcomes • Study limitations of observational medical records database studies includes misclassifications in admission diagnosis and absence of adequate compliance determination, among others.			⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings are derived from evidence that has not been peer reviewed or published.

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

Explanations

a. Rates derived from arms of RCTs are observational in nature (and indirect as it relates to the PICO question) as no comparative effectiveness of repeat treatment in viral rebound was found.
b. No comparative effectiveness available

References

1. Anderson AS, Caubel P, Rusnak JM, Investigators E-HT. Nirmatrelvir-Ritonavir and Viral Load Rebound in Covid-19. N Engl J Med **2022**; 387(11): 1047-9.
2. Wong CKH, Lau KTK, Au ICH, et al. Viral burden rebound in hospitalised patients with COVID-19 receiving oral antivirals in Hong Kong: a population-wide retrospective cohort study. Lancet Infect Dis **2023**.
3. Malden DE, Hong V, Lewin BJ, et al. Hospitalization and Emergency Department Encounters for COVID-19 After Paxlovid Treatment - California, December 2021-May 2022. MMWR Morb Mortal Wkly Rep **2022**; 71(25): 830-3.
4. Ranganath N, O'Horo JC, Challener DW, et al. Rebound Phenomenon After Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease 2019 (COVID-19) in High-Risk Persons. Clin Infect Dis **2023**; 76(3): e537-e9.

References

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™. Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.
2. Liu J, Pan X, Zhang S, et al. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac **2023**; 33: 100694.
3. U.S. Food and Drug Administration. Important Paxlovid™ EUA Dispensing Information for Patients with Moderate Renal Impairment. Available at: https://www.fda.gov/media/155072/download. Accessed 3 November 2022.
4. Anderson AS, Caubel P, Rusnak JM, Investigators E-HT. Nirmatrelvir-Ritonavir and Viral Load Rebound in Covid-19. N Engl J Med **2022**; 387(11): 1047-9.
5. Wong CKH, Lau KTK, Au ICH, et al. Viral burden rebound in hospitalised patients with COVID-19 receiving oral antivirals in Hong Kong: a population-wide retrospective cohort study. Lancet Infect Dis **2023**.
6. Wang L, Berger NA, Davis PB, Kaelber DC, Volkow ND, Xu R. COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.06.21.22276724 [Preprint 22 June 2022].
7. U.S. Food and Drug Administration. FDA Briefing Document. Available at: https://www.fda.gov/media/166197/download. Accessed 20 March 2023.
8. Malden DE, Hong V, Lewin BJ, et al. Hospitalization and Emergency Department Encounters for COVID-19 After Paxlovid Treatment - California, December 2021-May 2022. MMWR Morb Mortal Wkly Rep **2022**; 71(25): 830-3.
9. Ranganath N, O'Horo JC, Challener DW, et al. Rebound Phenomenon After Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease 2019 (COVID-19) in High-Risk Persons. Clin Infect Dis **2023**; 76(3): e537-e9.

Supplementary Materials

Study characteristics

- **Table s1.** Should nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir be used for ambulatory or hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease?

Risk of bias

- **Table s2.** Risk of bias for randomized controlled studies (nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir in ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease)

Table s1. Should nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir be used for ambulatory or hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease?

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Pfizer-FDA EUA/ 2021 [1]	359 multi-national sites	RCT	2224 (1109/1115)	49	46 years	Ambulatory patients with mild to moderate symptoms at high risk for progression to severe disease who had confirmed SARS CoV-2 infection within 5 days prior to randomization	Nirmatrelvir 300 mg/Ritonavir 100 mg (or renally adjusted for moderate renal disease) every 12 hours for 5 days	Placebo	Neutralizing monoclonal antibody treatments were balanced in each group	Mortality COVID-19 related hospitalization Serious adverse events Proportion of patients requiring discontinuation for adverse events	Pfizer
Liu 2023 [2]	China/ 5 COVID-19-designated hospitals	Parallel RCT	264 (132/132)	46.2	Mean (SD): Paxlovid + standard care: 71.50 (11.61) Standard treatment: 69.20 (14.43)	Hospitalized patients aged from 18 to 90 years old, had severe comorbidities, confirmed SARSCoV-2 infection by positive of real-time PCR within the previous 48 h, duration from symptoms	Received Paxlovid at a dose of 300 mg nirmatrelvir [two tablets] + 100 mg ritonavir [one tablet], orally administered every 12 h for 5 days,	Standard care including: antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and nutrient support, etc.	Standard care including: antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy,	28-day all-cause mortality Risk of death assessed in subgroup participants based on the duration since	National Natural Science Foundation of China

						onset to hospital admission less than 5 days or the SARS-CoV-2 nucleic acid Ct value ≤ 25 by RT-PCR The severe patients were defined as patients with severity comorbidities, SOFA or Charlson score ≥2. Severe comorbidities were defined as immunosuppressive disease or immunosuppressive status, chronic obstructive pulmonary disease, hypertension complicated with target organ injury, acute and chronic cardiac insufficiency, chronic renal			and nutrient support, etc.	symptoms onset to hospital admission Body mass index Ct value of N and ORF1ab gene The total number of comorbidities Efficacy included in-hospital mortality The proportion of progress to severe COVID-19 within 14 days The proportion of acute exacerbation from the	

						insufficiency, etc.				chronic disease within 14 days SARS–CoV-2 RNA clearance within 7 days and 14 days The duration of SARS–CoV-2 RNA clearance, length of hospital and ICU stay, Organ support days to 28 days Adverse events occurring during and after treatment period	

Table s2. Risk of bias for randomized controlled studies (nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir in ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Pfizer/FDA EUA 2021 [1]							
Liu 2023 [2]							

Low	High	Unclear

References for Supplementary Materials

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™. Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.
2. Liu J, Pan X, Zhang S, et al. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac **2023**; 33: 100694.