Nirmatrelvir/Ritonavir

Section last reviewed and updated 12/29/2021

Last literature search conducted 12/28/2021

Resources:

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

Recommendation 1 (NEW): 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 (i.e., medication reconciliation). Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.
- 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 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 for reasons other than COVID-19 may also receive nirmatrelvir/ritonavir
- Options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, 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.

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 U.S. Food and Drug Administration (FDA) granted emergency use authorization (EUA) to nirmatrelvir/ritonavir on December 22, 2021, for the treatment of mild to moderate COVID-19 in adults and pediatric patients 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]. Data have not yet been published, but data to prepare this recommendation was extracted from the FDA EUA document.

Benefits

Nirmatrelvir/ritonavir

All-cause mortality through day 28 may be lower in patients receiving nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir (RR: 0.04; 95% CI: 0.00, 0.69; low certainty of evidence [CoE]). Patients treated with nirmatrelvir/ritonavir rather than no nirmatrelvir/ritonavir may have fewer COVID-19-related hospitalizations (RR: 0.15; 95% CI: 0.07, 0.31; 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).

Harms

Nirmatrelvir/ritonavir

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 speed up 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
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

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.

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, phenytoin
- 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 22 December 2021.

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) will need to be counseled that they will only take one 150 mg nirmatrelvir tablet (oval shape, pink) with one 100 mg of ritonavir twice daily, instead of the regular dose of two 150 mg nirmatrelvir (300 mg) tablets with one 100 mg of ritonavir twice daily. When dispensing the product for patients with moderate renal impairment, pharmacists are instructed to alter the blister cards to ensure that patients receive the correct dose. Pharmacists need to adhere to the specific instructions when dispensing the product according to instructions provided in the EUA [2]. 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) and 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 is therefore not recommended in this population.

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

Other considerations

Nirmatrelvir/ritonavir

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.

Conclusions and research needs for this recommendation

Nirmatrelvir/ritonavir

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 5 days of symptom onset. More data are needed on the potential adverse effects of this medication.

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

New evidence profile developed 12/23/2021

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%)	54/1046 (5.2%)	**RR 0.15** (0.07 to 0.31)	**44 fewer per 1,000** (from 48 fewer to 36 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 SAEs 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.
f. Differential post randomization event exclusions (1040 patients) in the original phase (patients without risk factors) is unknown. Publication did not provide an intention to treat analysis. Not rated down for risk of bias as the data in this evidence profile is limited to the amended phase 1,200 mg dose only and not the entire data set (1,200 mg is the currently recommended dose). However, sensitivity analysis of the entire data set showed similar results: for hospitalizations 23/2091 vs 59/1341; RR 0.25 (95% CI 0.16, 0.4); deaths: 2/2091 vs 3/1341; RR 0.43 (95% CI 0.08, 2.3).

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

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. 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 22 December 2021.

Supplementary Materials

Study characteristics

- **Table s1.** Nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease

Risk of bias

- **Table s2.** Randomized controlled studies (nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir)

Table s1. Should nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir be used for ambulatory 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

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]							

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.