

Drug Class Review: COVID-19 Antivirals

Date of Review: April 2024

End Date of Literature Search: 10/04/2023

Purpose for Class Review:

Evaluate the efficacy, effectiveness and safety of antivirals approved or authorized to treat coronavirus disease 2019 (COVID-19) in non-hospitalized patients.

Plain Language Summary:

- Coronavirus disease 2019 (COVID-19) is caused by a virus called SARS-CoV-2. Most people who get infected with the virus will have mild to moderate symptoms and recover without needing treatment. People over 50 years of age, those that are not vaccinated, and people with certain medical conditions such as cancer, asthma, diabetes, obesity, or heart disease may be at risk for getting severe COVID-19 and may benefit from treatment with medicine.
- Two medicines called PAXLOVID (nirmatrelvir with ritonavir) and LAGEVRIO (molnupiravir) are pills that can be taken by mouth twice a day over 5 days. A third medicine called VEKLURY (remdesivir) must be given through a vein by infusion once a day over 3 days.
- These medicines have shown to lower the risk of getting hospitalized or dying from COVID-19 in people who have mild or moderate symptoms of COVID-19 and are at risk of severe disease. Real world studies continue to show how effective these medicines are as the virus continues to evolve and people's immunity to the virus changes, either from vaccination or past infections.
- PAXLOVID and LAGEVRIO should be started no later than 5 days after symptoms first appear. Remdesivir should be started no later than 7 days after the first symptoms appear. All 3 medicines must be prescribed by a healthcare provider. Pharmacists have Food and Drug Administration approval to prescribe PAXLOVID if the infection is confirmed by testing.
- There are special considerations that the healthcare provider uses to determine which treatment is best for each person. For example, PAXLOVID can interact with several other medicines in ways that can cause dangerous side effects. LAGEVRIO can harm an unborn baby and is not recommended for use during pregnancy. LAGEVRIO may affect bone growth and cannot be used in growing children.
- It is recommended that these medicines be available for people enrolled in the Oregon Health Plan (OHP) fee-for-service program.

Research Questions:

1. What is the evidence for efficacy of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir in treating COVID-19 infections?
2. What are the harms associated with the use of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir when used to treat COVID-19 infections?
3. Are there specific subpopulations that would be more likely to benefit from the use of one antiviral agent over another to treat COVID-19 infections?

Conclusions:

- Two systematic reviews^{1,2} and 3 clinical guidelines³⁻⁵ provide high-quality evidence for the efficacy and safety of ritonavir-boosted nirmatrelvir, molnupiravir, and remdesivir for treatment of COVID-19 infection.

- A 2023 Cochrane systematic review evaluated all published evidence for the effects of remdesivir on improving clinical outcomes in COVID-19.¹ However, only one RCT (n=562) was conducted in non-hospitalized patients. Participants of that RCT had mild or moderate symptoms that had started 4 days or less prior to screening, and were at risk of progression to severe COVID-19.¹ The primary outcome was a composite of hospitalization related to COVID-9 or death from any cause by day 28. This trial showed that remdesivir decreased the risk of hospitalization up to day 28 compared with placebo (RR 0.28, 95% CI, 0.11 to 0.75; moderate-certainty evidence).¹ No deaths were reported in either arm of this study, so it was not possible to determine if remdesivir impacts 28-day mortality.¹ There were less serious adverse events in the remdesivir arm compared with placebo arm (RR 0.27, 95% CI, 0.10 to 0.70; low-certainty evidence), but no differences in AE of any grade were found between arms (RR 0.91, 95% CI 0.76 to 1.10; moderate-certainty evidence).¹
- A 2022 Cochrane systematic review assessed the efficacy and safety of ritonavir-boosted nirmatrelvir in treating mild or moderate COVID-19 infection.² One RCT (n=2,246) conducted in non-hospitalized patients that compared ritonavir-boosted nirmatrelvir with placebo met inclusion criteria.² Trial participants were unvaccinated, without previous confirmed SARS-CoV-2 infection, onset of symptoms of no longer than 5 days, and were at high risk for progression to severe disease.² The trial found that ritonavir-boosted nirmatrelvir may reduce all-cause mortality at 28 days versus placebo (RR 0.04, 95% CI, 0.00 to 0.68; low-certainty evidence), and reduce admission to hospital or death within 28 days (RR 0.13, 95% CI, 0.07 to 0.27; low-certainty evidence).² There were less serious adverse events with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 0.24, 95% CI, 0.15 to 0.41; low-certainty evidence).² No difference in overall treatment-emergent adverse events were found between arms (RR 0.95, 95% CI, 0.82 to 1.10; moderate-certainty evidence).² However dysgeusia and diarrhea were more likely to occur with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 2.06, 95% CI, 1.44 to 2.95; moderate-certainty evidence).²
- The National Institute of Health (NIH) recommendations for treatment of non-hospitalized adults with COVID-19 are as follows:
 - Oral ritonavir-boosted nirmatrelvir is favored in most high-risk, non-hospitalized adults with mild to moderate symptoms of COVID-19 (Strong Recommendation, Moderate-quality Evidence).³
 - Intravenous remdesivir is recommended when ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions) (Moderate Recommendation, Moderate-quality Evidence).³
 - Oral molnupiravir is an alternative therapy, for use when the preferred therapies are not available, feasible to use, or clinically appropriate (Weak Recommendation, Moderate-quality Evidence).³ The NIH panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (Strong Recommendation, Expert Opinion).³
- The Infectious Diseases Society of America (IDSA) recommendations for treatment of non-hospitalized people with COVID-19 are as follows:
 - Remdesivir if initiated within 7 days of symptom onset rather than no remdesivir. (Conditional Recommendation, Low Certainty of Evidence).⁴
 - Ritonavir-boosted nirmatrelvir if initiated within 5 days of symptom onset rather than no ritonavir-boosted nirmatrelvir. (Conditional Recommendation, Low Certainty of Evidence).⁴
 - For adults age 18 years or older who have no other treatment option, molnupiravir if initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional Recommendation, Low Certainty of Evidence).⁴
- The National Institute of Health and Care Excellence (NICE) guidance is similar to the NIH and IDSA recommendations. Ritonavir-boosted nirmatrelvir or remdesivir are considered first- and second-line treatments, respectively, in non-hospitalized adults with mild-to-moderate COVID-19 who are at high risk for progression to severe disease.⁵ Molnupiravir is considered a third-line treatment in adults who have no other treatment option.⁵
- Guidance for use in special populations is as follows:
 - Remdesivir is Food and Drug Administration (FDA)-approved for treatment of COVID-19 in pediatric patients aged 28 days and older.⁶
 - Ritonavir-boosted nirmatrelvir is FDA-approved for treatment of COVID-19 in adults.⁷
 - Ritonavir-boosted nirmatrelvir is approved via an FDA emergency use authorization (EUA) for use in pediatric patients aged 12 years and older.⁸

- Ritonavir-boosted nirmatrelvir should not be initiated in patients taking concomitant medications highly dependent on CYP3A4 metabolism until the risk for significant drug interactions is assessed and a plan implemented to prevent adverse reactions.⁷
- The dose of ritonavir-boosted nirmatrelvir should be reduced in patients with impaired renal function (i.e., estimated glomerular filtration rate [eGFR] 30 to 60 mL/min).⁷ Ritonavir-boosted nirmatrelvir is not recommended for patients with severe renal impairment (i.e., eGFR < 30 mL/min).⁷
- Molnupiravir is available via an FDA EUA for treatment of COVID-19 in adults.⁹
- Molnupiravir is not authorized under the FDA EUA for use in patients younger than 18 years of age because it may affect bone and cartilage growth.⁹
- Molnupiravir is not recommended for pregnant individuals due to the risk of fetal harm observed in animal models.⁹
- People who are members of racial and ethnic minority groups have higher rates of hospitalization and death from COVID-19 than people who are White.³ Disparities in the use of antiviral treatments in patients who are not White have been reported; therefore, attention to equitable access is critical.³ In outpatient studies of the 3 COVID-19 antivirals, Black, Asian, Hispanic, and American Indian populations were underrepresented (see **Table 2**).

Recommendations:

- Create a Preferred Drug List (PDL) class for the antivirals FDA-approved to treat COVID-19 infection and designate ritonavir-boosted nirmatrelvir and remdesivir as preferred agents on the PDL. Ritonavir-boosted nirmatrelvir is only FDA-approved in adults, therefore access for pediatric patients aged 12 to 18 years is only available through the FDA EUA.
- Since molnupiravir is only available through EUA, it will not have PDL status until it is FDA-approved. If it receives FDA-approval, recommend making molnupiravir preferred on the PDL with age restrictions in patients aged 17 years and younger due to risk of adverse effects.

Background:

COVID-19 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).³ According to the Centers for Disease Control and Prevention (CDC), over one million people have died from COVID-19 in the United States.¹⁰ The NIH has stratified the severity of COVID-19 into four levels:

1. Mild disease: Individuals have symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.³
2. Moderate disease: Individuals show evidence of lower respiratory tract disease and have oxygen saturation measured by pulse oximetry (SpO₂) ≥ 94% on room air.³
3. Severe disease: Individuals have pneumonia and one of the following: SpO₂ < 94% on room air, respiratory rate > 30 breaths/minute, or lung infiltrates > 50%.³
4. Critical disease: Individuals have respiratory failure, septic shock, and/or multiple organ dysfunction.³

Most symptomatic COVID-19 patients have mild or moderate disease and do not require hospitalization.¹¹ Patients who develop severe or critical disease require hospitalization with respiratory support.¹¹ Many factors can increase the risk for developing severe or critical COVID-19 disease.¹¹ Some of the most common risk factors are age over 50 years, obesity, cardiovascular disease, asthma, and chronic obstructive pulmonary disease.^{3,11} Communities that have been historically marginalized or made socially vulnerable due to a lack of access to health care or an inability to socially isolate are at increased risk of SARS-CoV-2 acquisition, COVID-19–related hospitalization, and death.^{3,11} These communities include racial and ethnic minorities, essential non-health care workers, and some people with disabilities.^{3,11} The severity of COVID-19 is changing as the proportion of individuals who are vaccinated increases and the prevalence of different SARS-CoV-2 variants changes.¹²

Three antiviral agents are currently available for treatment of SARS-CoV-2 infection. Ritonavir-boosted nirmatrelvir (PAXLOVID) is a combination oral drug that inhibits 3-chymotrypsin-like cysteine protease, an enzyme necessary to produce other functional SARS-CoV-2 proteins.¹² Ritonavir does not have anti-SARS-CoV-2 activity, but is used as a pharmacokinetic booster to slow the metabolism of nirmatrelvir and allow for twice daily dosing.¹² Ritonavir-boosted nirmatrelvir tablets are FDA-approved for treatment of adults with mild-to-moderate COVID-19 infection who are at risk for severe COVID-19 and hospitalization.⁷ Ritonavir-boosted nirmatrelvir is available via the FDA EUA for pediatric patients aged 12 to 17 years, and its use must be consistent with the terms and conditions of the EUA.⁸

A second oral antiviral, molnupiravir (LAGEVRIO) is a prodrug of N-hydroxycytidine (NHC), an oral ribonucleoside analog that causes viral genome replication errors.¹² Molnupiravir has FDA EUA for use in adults with mild-to-moderate symptoms of COVID-19 who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.⁹

The third antiviral, remdesivir (VEKLURY) is administered via intravenous (IV) infusion. Remdesivir is a nucleotide prodrug of an adenosine analog, and binds to the viral RNA-dependent RNA polymerase which inhibits viral replication by prematurely terminating RNA transcription.⁶ Remdesivir is FDA-approved for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are: 1) hospitalized, or 2) not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.⁶

A comparison of the 3 antiviral indications and dosing is presented in **Table 1**. Additional details including pharmacology, pharmacokinetics, warnings, precautions and use in special populations for each drug are summarized in **Appendix 1**.

Table 1. Antivirals to Treat Mild-to-Moderate COVID-19 in People at High Risk for Progression to Severe COVID-19 Disease.

Drug Name (Brand Name, Manufacturer)	FDA Approval or FDA EUA	Age Range	Route/Strength	Dose and Frequency
Molnupiravir ⁹ (LAGEVRIO, Merck)	<ul style="list-style-type: none"> EUA effective 12/23/2021. 	<ul style="list-style-type: none"> Adults 	<ul style="list-style-type: none"> Oral 200 mg capsules 	<ul style="list-style-type: none"> Four x 200 mg capsules orally every 12 hours x 5 days Start within 5 days of symptom onset.
Nirmatrelvir (Ritonavir-boosted) ^{7,8} (PAXLOVID, Pfizer)	<ul style="list-style-type: none"> FDA approval 5/25/2023 for adults. EUA effective 12/22/2021 and continues to authorize eligible pediatric patients not covered under the FDA approval. 	<ul style="list-style-type: none"> FDA-approved: Adults EUA: Children aged 12 to 18 years weighing at least 40 kg 	<ul style="list-style-type: none"> Oral Nirmatrelvir 150 mg with Ritonavir 100 mg tablets co-packaged 	<ul style="list-style-type: none"> Two nirmatrelvir 150 mg tablets with one ritonavir 100 mg tablet orally twice daily x 5 days. For patients with moderate renal impairment (eGFR 30 to 59 mL/min): Reduce dose to one nirmatrelvir 150 mg with one ritonavir 100 mg tablet orally twice daily for 5 days. Not recommended in patients with severe renal impairment (eGFR <30 mL/min).

				<ul style="list-style-type: none"> • Not recommend in patients with severe hepatic impairment (Child-Pugh Class C). • Start within 5 days of symptom onset.
Remdesivir ⁶ (VEKLURY, Gilead)	<ul style="list-style-type: none"> • FDA approval 10/22/2020. 	<ul style="list-style-type: none"> • Adults and children 28 days of age and older and weighing at least 3 kg 	<ul style="list-style-type: none"> • Intravenous infusion • 100 mg vial 	<ul style="list-style-type: none"> • 200 mg IV on day 1 followed by 100 mg IV for 2 consecutive days. • Pediatric dose is 5 mg/kg on day 1 followed by 2.5 mg/kg on days 2 and 3. • Start within 7 days of symptom onset.
Abbreviations: eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; kg = kilograms; mg = milligrams; mL = milliliters; min = minutes.				

Differences in participants studied across the COVID-19 antiviral RCTs do not permit direct comparisons or formal quantitative indirect comparisons of safety and effectiveness between the 3 antivirals currently recommended for COVID-19 treatment.¹² For example, the molnupiravir trial enrolled substantially larger proportions of individuals with obesity compared to the nirmatrelvir/ritonavir trial.¹³ In addition, there were variabilities in the timing of trial enrollment which affected the primacy causal variant observed in the trials and impacted the vaccination status of study participants between trials.¹² Factors that must be considered when reviewing these trials include: 1) the rapid evolution of SARS-CoV-2 leading to variants with treatment resistance and with different morbidity and mortality impacts; 2) the enrollment of predominantly unvaccinated patients in early trials; and 3) the uncertain generalizability of data related to hospitalization rates and other health care resource utilization from studies conducted prior to the advent of the Omicron variant and based predominately or exclusively in countries outside of the United States (US).¹² An overview of the pivotal trials that provided safety and efficacy evidence for use of antivirals in treating COVID-19 is provided in **Table 2**. Currently, there are no comparative head-to-head trials for the 3 antivirals approved or authorized to treat COVID-19.

Table 2. Key RCTs in Outpatient Adults with Mild-to-Moderate COVID-19 at High Risk for Severe Disease.

Trial Details	Intervention	Inclusion/Exclusion Criteria	Outcomes	Baseline Characteristics	Results
Bernal A, et al. ¹³ MOVE-OUT <ul style="list-style-type: none"> • DB, MC, Phase 2/3 RCT • N=1,433 • 107 sites in 20 countries • Enrollment: 5/6/2021-10/2/2021 	1. Molnupiravir 800 mg orally twice daily x 5 days (n=709) Vs. 2. Placebo orally twice daily x 5 days (n=699)	Inclusion: <ul style="list-style-type: none"> • Age ≥18 yrs • Mild or moderate symptom onset within 5 days • Not vaccinated • ≥1 risk factor for severe disease Exclusion: <ul style="list-style-type: none"> • Unwillingness to use contraception during treatment and at least 4 days after treatment completion • Prior COVID-19 vaccination • HBV or HCV infection with complications 	Primary Endpoints: <ul style="list-style-type: none"> • Incidence of hospitalization or death from any cause through day 29 • Incidence of adverse events 	Age (median): 43 yrs Gender (female): 51% US enrollment: 6% Race/ethnicity: <ul style="list-style-type: none"> • 57% White • 7% American Indian • 7% Alaska Native • 5% Black • 3% Asian Risk factors: <ul style="list-style-type: none"> • BMI ≥30: 74% • Age >60 years: 17% • Diabetes: 16% 	Hospitalization or Death from any Cause through Day 29 <ol style="list-style-type: none"> 1. 6.8% (n=48) 2. 9.7% (n=68) Difference: -3.0% 95% CI, -5.9 to -0.1 Mortality <ol style="list-style-type: none"> 1. 0.1% (n=1) 2. 1.3% (n=9) Adverse Events <ol style="list-style-type: none"> 1. 1.4% (n=10) 2. 2.9% (n=20)

					Serious Adverse Events 1. 0.7% (n=5) 2. 1.9% (n=13)
Hammond J, et al. ¹⁴ EPIC-HR <ul style="list-style-type: none"> DB, MC, Phase 2/3 RCT N=2,246 343 sites in 21 countries Enrollment: 7/16/2021-12/9/2021 	1. Nirmatrelvir 300 mg with ritonavir 100 mg orally every 12 hours x 5 days (n=1039) Vs. 2. Placebo orally every 12 hours x 5 days (n=1046)	Inclusion: <ul style="list-style-type: none"> Age ≥18 yrs Mild or moderate symptom onset within 5 days Not vaccinated ≥1 risk factor for severe disease Exclusion: <ul style="list-style-type: none"> Prior COVID-19 infection or vaccination HIV infection 	Primary Endpoint: <ul style="list-style-type: none"> COVID-19-related hospitalization or death from any cause through day 28 Secondary Endpoints: <ul style="list-style-type: none"> Adverse events 	Age (median): 46 yrs Gender (female): 49.5% US enrollment: 41% Race/ethnicity: <ul style="list-style-type: none"> 72% White 5% Black 14% Asian 9% American Indian or Alaska Native Risk factors: <ul style="list-style-type: none"> BMI ≥30: 33% Age >60 years: 12% Diabetes: 12% Hypertension: 33% 	Hospitalization or Death from any Cause through Day 28 <ol style="list-style-type: none"> 0.77% (n=8) 6.31% (n=65) Difference: 5.62% 95% CI, 7.21 to 4.03 P< 0.001 Mortality <ol style="list-style-type: none"> 0% (n=0) 1.15% (n=12) Adverse Events <ol style="list-style-type: none"> 7.8% (n=86) 3.8% (n=42) Serious Adverse Events <ol style="list-style-type: none"> <0.1% (n=1) 0% (n=0)
Gottlieb RL, et al. ¹⁵ PINETREE <ul style="list-style-type: none"> DB, MC Phase 3 RCT N=562 64 sites in 4 countries Enrollment: 9/18/2020-4/8/2021 	1. Remdesivir 200 mg IV on Day 1 followed by 100 mg IV on Days 2 and 3 (n=279) Vs. 2. Placebo (n=283) IV on days 1-3	Inclusion: <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection ≤4 days from screening Aged ≥12 yrs ≥1 risk factor for disease progression or 60 yrs and older Symptom onset ≤7 days from randomization ≥1 ongoing COVID-19 symptom Exclusion: <ul style="list-style-type: none"> COVID-19 vaccination Receipt of supplemental oxygen Previous hospitalization or treatment for COVID-19 	Primary Endpoints: <ul style="list-style-type: none"> COVID-19-related hospitalization or death from any cause by Day 28 Occurrence of AEs 	Age (median): 50 yrs Gender (female): 48% Adolescents: 1.4% (n=8) US enrollment: 94% Race/ethnicity: <ul style="list-style-type: none"> 80% White 8% Black 6% American Indian 3% Asian 42% Hispanic Risk factors: <ul style="list-style-type: none"> BMI ≥30: 55% Age >60 years: 30% Diabetes: 62% Hypertension: 48% 	Hospitalization or Death from any Cause through Day 28 <ol style="list-style-type: none"> 0.7% (n=2) 5.3% (n=15) HR: 0.13 95% CI, 0.03 to 0.59 P=0.0008 Mortality <ol style="list-style-type: none"> 0 0 Adverse Events <ol style="list-style-type: none"> 12.2% (n=34) 8.8% (n=25) Serious Adverse Events <ol style="list-style-type: none"> 1.8% (n=5) 6.7% (n=19)

Abbreviations: BMI = body mass index; CI = Confidence Interval; COVID-19 = coronavirus disease; DB = double blind; HR = Hazard Ratio; HBV = hepatitis B; HCV = hepatitis C; IV = intravenous; LOS = length of stay; MC = multi-center; n = number; RCTs = randomized controlled trials; US = United States; WHO = World Health Organization; yrs = years

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, and warnings and precautions.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Remdesivir for Treatment Of COVID-19

A 2023 Cochrane systematic review evaluated all evidence from RCTs on the effect of remdesivir on clinical outcomes in COVID-19.¹ Literature was searched through May 21, 2022.¹ Non-hospitalized individuals with asymptomatic or mild COVID-19 infection were differentiated from hospitalized individuals with moderate to severe COVID-19.¹ Nine RCTs (n=11,218) met inclusion criteria, however only one (n=562) of the 9 RCTs was conducted in the outpatient setting in symptomatic people with a risk of progression to severe disease.¹ The population in the outpatient RCT differed significantly from the hospitalized population in terms of baseline disease severity, clinical course, and duration of the treatment (3 days versus 10 days, respectively), so the data were analyzed separately.¹ Risk of bias for the outpatient RCT was considered to be low for risk of hospitalization (clinical worsening) and safety outcomes.¹ Risk of bias for clinical improvement by day 14 was estimated as high as a large number of missing values and analyses were not performed as pre-defined by protocol, with a high risk of selective reporting.¹

Data from this RCT showed that remdesivir decreased the risk of hospitalization up to day 28 compared with placebo (RR 0.28, 95% CI, 0.11 to 0.75; risk difference [RD] 46 fewer per 1000, 95% CI, 57 fewer to 16 fewer; n=562; moderate-certainty evidence).¹ No deaths were reported in either arm of this study, so it was not possible to determine if remdesivir impacts 28-day mortality.¹ There were less serious adverse events (in the remdesivir arm compared with placebo arm (RR 0.27, 95% CI, 0.10 to 0.70; low-certainty evidence), but no differences in AE of any grade were found between arms (RR 0.91, 95% CI 0.76 to 1.10; moderate-certainty evidence).¹ The applicability of this evidence to current practice may be limited by the recruitment of participants from mostly unvaccinated populations exposed to early variants of the SARS-CoV-2 virus at the time the study was undertaken.¹

Nirmatrelvir Combined with Ritonavir for Treatment of COVID-19

A 2022 Cochrane systematic review assessed the efficacy and safety of ritonavir-boosted nirmatrelvir in treating COVID 19.² Literature was searched through July 11, 2022. Only one trial (n=2,246) met inclusion criteria, an RCT conducted in outpatients with mild to moderate COVID-19 which compared ritonavir-boosted

nirmatrelvir with standard of care plus placebo.² Trial participants were unvaccinated, without previous confirmed SARS-CoV-2 infection, had a symptom onset of no more than 5 days before randomization, and were at high risk for progression to severe disease.² No evidence is currently available on ritonavir-boosted nirmatrelvir to treat hospitalized people with COVID-19 or to prevent a SARS-CoV-2 infection.

Ritonavir-boosted nirmatrelvir compared to standard of care plus placebo may reduce all-cause mortality at 28 days (RR 0.04, 95% CI, 0.00 to 0.68; 1 study, n= 2,224; estimated absolute effect: 11 deaths per 1000 people receiving placebo compared to 0 deaths per 1000 people receiving nirmatrelvir/ritonavir; low-certainty evidence), and may reduce hospitalization or death within 28 days (RR 0.13, 95% CI, 0.07 to 0.27; estimated absolute effect: 61 admissions or deaths per 1000 people receiving placebo compared to 8 admissions or deaths per 1000 people receiving nirmatrelvir/ritonavir; low-certainty evidence).²

There were less serious adverse events with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 0.24, 95% CI, 0.15 to 0.41; low-certainty evidence).² No difference in overall treatment-emergent adverse events were found between arms (RR 0.95, 95% CI, 0.82 to 1.10; moderate-certainty evidence).² However dysgeusia and diarrhea were more likely to occur with ritonavir-boosted nirmatrelvir compared to standard of care plus placebo (RR 2.06, 95% CI, 1.44 to 2.95; moderate-certainty evidence).²

In summary, there is low-certainty evidence that ritonavir-boosted nirmatrelvir reduces the risk of all-cause mortality and hospital admission or death based on one trial investigating unvaccinated COVID-19 participants with symptom onset of no more than 5 days, without previous infection, who were at high risk for progression to severe disease.²

After review, 10 systematic reviews were excluded due to poor quality (e.g., network meta-analyses),¹⁶⁻²² or wrong study design of included trials (e.g., observational).²³⁻²⁶

Guidelines:

National Institute of Health: Therapeutic Management of Nonhospitalized Adults with COVID-19

The most recent NIH update on treatment of outpatients with COVID-19 was issued July 21, 2023.³ The NIH recommends that several factors be considered before treatment is selected for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications, the potential for significant drug-drug interactions, the patient's pregnancy status, time from symptom onset, and the *in vitro* activity of the available drug against currently circulating SARS-CoV-2 variants and subvariants.³ Most of the data that support the use of the recommended treatment options come from clinical trials that enrolled individuals who were at high risk of disease progression and who had no pre-existing immunity from COVID-19 vaccination or prior SARS-CoV-2 infection.³ The proportion of hospitalizations and deaths in the placebo arms of these trials was high compared to what is observed currently in populations where most people are vaccinated or have had prior SARS-CoV-2 infection.³ Although these trials demonstrated the efficacy of using antiviral drugs in high-risk populations, it is difficult to know their precise effectiveness in the current real-world settings.³

Available therapies remain beneficial in people who continue to have an increased risk of disease progression.³ These risk factors of severe disease include older people (i.e., those aged >50 years, but especially those aged ≥65 years) and people who are unlikely to have an adequate immune response to COVID-19 vaccines due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications.³ Other risk factors include lack of vaccination or incomplete vaccination; a prolonged amount of time since the most recent vaccine dose (e.g., >6 months); and conditions such as obesity, diabetes, and chronic respiratory, cardiac, or kidney disease.^{1 3} Recommendations for patients who are at high risk for progressing to severe COVID-19 are as follows in order of preference:

- Oral ritonavir-boosted nirmatrelvir is favored in most high-risk, nonhospitalized patients with mild to moderate COVID-19 (Strong Recommendation, Moderate-quality Evidence).³
 - Ritonavir-boosted nirmatrelvir has high efficacy and has been shown to reduce hospitalization and death when administered to high-risk, unvaccinated, nonhospitalized patients within 5 days of symptom onset.^{3,14}
 - Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions.³
 - The use of ritonavir-boosted nirmatrelvir may be challenging in patients with severe renal impairment and in patients receiving certain transplant-related immunosuppressants or chemotherapy.³
- Intravenous remdesivir is recommended when ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions) (Moderate Recommendation, Moderate-quality Evidence).³
- Oral molnupiravir is recommended to be reserved as alternative therapy when preferred therapies are not available, feasible to use, or clinically appropriate (Weak Recommendation, Moderate-quality Evidence).³
 - Molnupiravir appears to have lower efficacy¹³ than the other options recommended by the NIH Panel, although no RCTs have directly compared these therapies.³
 - The NIH panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (Strong Recommendation, Expert Opinion).³

Infectious Diseases Society of America: Treatment of Patients with COVID-19

In March 2020, the IDSA formed a multidisciplinary guideline panel of infectious diseases clinicians, pharmacists, and methodologists with varied areas of expertise to regularly review the evidence and make recommendations about the treatment and management of persons with COVID-19.⁴ The process used a living guideline approach and followed a rapid recommendation development checklist.⁴ The most recent treatment update was published April 12, 2023. After a review of published evidence, medications that are **not** recommended for outpatient treatment of COVID-19 include: hydroxychloroquine, chloroquine, azithromycin, lopinavir/ritonavir, inhaled corticosteroids, famotidine, ivermectin, and colchicine.⁴ The antidepressant, fluvoxamine, is recommended only in the context of a clinical trial (no recommendation; insufficient evidence).⁴ In 2 RCTs that studied symptomatic ambulatory patients with COVID, fluvoxamine failed to demonstrate a beneficial effect on mortality at 28 days compared to no fluvoxamine (RR 0.69; 95% CI, 0.38 to 1.27; low-quality evidence).⁴

The overall certainty of evidence for the use of remdesivir in patients with mild-to-moderate COVID-19 was low due to concerns about imprecision, as less than half of the original projected sample size was enrolled leading to few events and fragility of the effect estimate.⁴ However, compared to prior trials, giving remdesivir early in the course of infection appears to have a robust effect within the limitation of a small sample size.⁴ The panel agreed that benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk for severe disease.⁴ The evidence confirms that using remdesivir early in the disease process when viral loads are high confers maximum benefit.⁴ The evidence for the use of remdesivir in children is limited.⁴ For ambulatory children at risk for severe disease, one RCT included 8 children aged 12 to 18 years, limiting confidence in the available direct evidence for ambulatory care.⁴ A report of 77 children who received remdesivir through compassionate use early in the pandemic found good tolerability in this population with a low rate of serious adverse events.⁴

The overall certainty of the evidence for the use of ritonavir-boosted nirmatrelvir in ambulatory patients is low. There are concerns with the inability to exclude potential risks to bias because of limited availability of study details, and there is imprecision due to a low number of events reported.⁴ 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.⁴ The evidence confirms that using ritonavir-boosted nirmatrelvir early in the disease process when viral loads are high confers maximum benefit.⁴ Recurrence of symptoms associated with viral rebound has been estimated to occur in ritonavir-boosted nirmatrelvir- treated patients in 0.8% to 6.6% in various trials, including the EPIC-HR trial.^{4,14} More data are needed on the potential adverse effects of this medication.⁴ In addition, future studies are important to inform the impact of ritonavir-boosted nirmatrelvir in hospitalized patients, in vaccinated high-risk patients with mild-to-moderate COVID-19 and in symptomatic immunocompromised patients with persistently elevated viral loads.⁴

The overall certainty of evidence for the use of molnupiravir in ambulatory patients is low given concerns with data imprecision, driven by few reported events and a relatively small effect size.⁴ The use of molnupiravir presents additional considerations and potential concerns regarding viral mutagenesis in immunocompromised persons and safety in persons of reproductive age, for which more data are needed to quantify such effects.⁴ The panel recognized that alternative treatment options exist with the possibility of greater benefit with a smaller known safety profile.⁴ The guideline panel suggests the use of molnupiravir 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 and have no other treatment options.⁴ More data are needed on the potential adverse effects of molnupiravir.⁴

Conditional recommendations supporting the use of remdesivir, ritonavir-boosted nirmatrelvir, and molnupiravir based on low-quality evidence are summarized below. Patient-specific factors (e.g., patient age, symptom duration, renal function, drug interactions), product availability, and institutional capacity and infrastructure should drive decision-making regarding choice of agent.⁴ It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.⁴ Data for combination of treatments do not currently exist.⁴

- Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at high risk for progression to severe disease (e.g., patients with SpO₂ ≤ 94% on room air), the IDSA guideline panel suggests remdesivir initiated within 7 days of symptom onset rather than no remdesivir. (Conditional Recommendation, Low Certainty of Evidence).⁴
 - Dosing for remdesivir in mild-to-moderate COVID-19 is 200 mg on day one followed by 100 mg on days two and three. Pediatric dosing is 5 mg/kg on day 1 and 2.5 mg/kg on subsequent days.⁴
- In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests ritonavir-boosted nirmatrelvir initiated within 5 days of symptom onset rather than no ritonavir-boosted nirmatrelvir. (Conditional Recommendation, Low Certainty of Evidence).⁴
 - Drug/supplement screening needed for potential drug interactions.⁴
 - Dosing based on renal function per manufacturer's guidance.⁴
- In ambulatory patients (≥18 years of age) with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment option, the IDSA guideline panel suggests molnupiravir initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional Recommendation, Low Certainty of Evidence).⁴
 - Molnupiravir is not authorized under the FDA EUA for use in pediatric patients less than 18 years because it may affect bone and cartilage growth.⁴
 - Molnupiravir is not authorized under the FDA EUA for use during pregnancy.⁴

National Institute for Health and Care Excellence: Managing COVID-19 Rapid Guideline

The NICE guidance was published in March 2021 and most recently updated June 22, 2023.⁵ Risk factors for progression to severe COVID-19 in adults were defined by the independent advisory group and include: people with Down's syndrome and other genetic disorders, solid cancer, hematological diseases and

recipients of hematological stem cell transplant, renal disease, liver diseases , solid organ transplants, immune-mediated inflammatory disorders, asthma, chronic pulmonary obstructive disease, immune deficiencies, HIV/AIDS, and neurological disorders.⁵ Most of the RCTs reviewed for the NICE guidance were in unvaccinated patients prior to the emergence of the Omicron variant (see **Table 2** above).⁵

- Ritonavir-boosted nirmatrelvir is recommended as first-line treatment initiated as soon as possible and within 5 days of symptom onset (benefits outweigh harms for almost everyone) for treating COVID-19 in adults, only if the patient is at increased risk for progression to severe COVID-19, as described earlier, and supplemental oxygen for the infection is not needed.⁵
- Remdesivir is recommended as a second-line treatment option (Conditional recommendation; benefits outweigh harms for most people). A 3-day course of remdesivir may be considered for children and young people who weigh at least 40 kg and adults with COVID-19 who:
 - do not need supplemental oxygen for COVID-19, and
 - are within 7 days of symptom onset, and
 - are thought to be at high risk of progression to severe COVID-19.⁵
- Molnupiravir may be considered as a third-line treatment option (Conditional recommendation) for adults with COVID-19 who:
 - do not need supplemental oxygen for COVID-19, and
 - are within 5 days of symptom onset, and
 - are thought to be at high risk of progression to severe COVID-19.⁵

Randomized Controlled Trials:

A total of 365 citations were manually reviewed from the initial literature search. After further review, 365 citations were excluded because of wrong study design, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Specific Drug Information

Table 1. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption/Distribution	Metabolism/Excretion	Pharmacokinetics (mean)
Molnupiravir (LAGEVRIO)⁹	<ul style="list-style-type: none"> Prodrug metabolized to NHC, a nucleoside analog which inhibits RNA replication. 	<ul style="list-style-type: none"> Median T_{max} = 1.5 hrs 0% protein bound 	<ul style="list-style-type: none"> Major route of elimination is hepatic. 	<ul style="list-style-type: none"> Half-life: 3.3 hrs Cmax: 2330 ng/mL AUC: 8260 ng/hr/ml Vd: 142 L
Nirmatrelvir/Ritonavir (PAXLOVID)⁷	<ul style="list-style-type: none"> Nirmatrelvir: protease inhibitor which blocks viral replication. Ritonavir: inhibits metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. It does not have viral activity against the SARS-CoV-2 virus. 	<ul style="list-style-type: none"> Median T_{max} = 3 hrs 69% protein bound 	<ul style="list-style-type: none"> Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal. Major route of elimination is renal. 	<ul style="list-style-type: none"> Half-life: 6.05 hrs Cmax: 3.43 mcg/mL AUC: 30.4 mcg/hr/mL Vd: 104.7 L
Remdesivir (VEKLURY)⁶	<ul style="list-style-type: none"> Nucleotide analog RNA polymerase inhibitor which reduces RNA transcription. 	<ul style="list-style-type: none"> T_{max} = 0.67 to 0.68 hrs 88-93.6% protein bound 	<ul style="list-style-type: none"> Major route of elimination is hepatic. Metabolic Pathways <ul style="list-style-type: none"> ○ CES1 80% ○ Cathepsin A (10%) ○ CYP3A 10% 	<ul style="list-style-type: none"> Half-life: 1 hr Cmax: 2229 ng/L AUC: 1585 ng/hr/mL Vd: NR
Abbreviations: AUC = area under the curve; C = concentration; CYP = cytochrome P450; hrs = hours; L = liters; mcg = micrograms; mL = milliliters; ng = nanograms; NHC = N-hydroxycytidine; NR = not reported; T = time; Vd = volume of distribution				

Table 2. Use in Specific Populations.

Drug Name	Pediatric Patients	Patients with Renal Impairment	Patients with Hepatic Impairment	Pregnancy/Lactation
Molnupiravir (LAGEVRIO)⁹	<ul style="list-style-type: none"> Not authorized for use in patients < 18 yo as it may affect bone and cartilage growth. 	<ul style="list-style-type: none"> No dose adjustment is recommended. 	<ul style="list-style-type: none"> No dose adjustment is recommended. 	<ul style="list-style-type: none"> Based on animal data, may cause fetal harm. Use is not recommended during pregnancy. Breast feeding is not recommended during treatment and up until 4 days after last dose.
Nirmatrelvir/Ritonavir (PAXLOVID)⁷	<ul style="list-style-type: none"> EUA permits use in pediatric patients > 12 yo and older weighing at least 40 kg Not FDA approved in patients < 18 yo 	<ul style="list-style-type: none"> Moderate renal impairment (eGFR 30 to 59 mL/min): reduce dose to 2 tablets (nirmatrelvir 150 mg with 1 tablet of ritonavir 100 mg) orally twice daily for 5 days. Not recommended in severe renal impairment (eGFR <30 mL/min) 	<ul style="list-style-type: none"> No dose adjustment is recommended in mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Not recommended for use in severe hepatic impairment (Child-Pugh Class C) due to lack of data. 	<ul style="list-style-type: none"> Insufficient data to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse fetal outcomes. Insufficient data in breast fed infants. Consider risk versus benefit.
Remdesivir (VEKLURY)⁶	<ul style="list-style-type: none"> Approved in pediatric patients 28 days of age and older and weighing at least 3 kg. 	<ul style="list-style-type: none"> No dose adjustment is recommended. 	<ul style="list-style-type: none"> No dose adjustment is recommended. Discontinue if ALT/AST increase to > 10 times the upper limit of normal 	<ul style="list-style-type: none"> Insufficient pregnancy data is available during first trimester. No drug-associated risks have been identified in second and third trimesters. Consider risk versus benefit in lactation.

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration; EUA = Emergency Use Authorization; FDA = Food and Drug Administration kg = kilograms; mg = milligram; mL = milliliters; min = minutes; yo = years old

Table 3. Summary of Warnings and Precautions.

Drug Name	Drug Interactions	Hepatic Disease	Risk of HIV-1 Resistance
Molnupiravir (LAGEVRIO)⁹	N/A	N/A	N/A
Nirmatrelvir/Ritonavir (PAXLOVID)⁷	<ul style="list-style-type: none"> Contraindicated for co-administration with drugs metabolized by CYP3A hepatic pathway. 	<ul style="list-style-type: none"> Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Caution should be exercised in patients with pre-existing hepatic disease, liver enzyme abnormalities, or hepatitis. 	<ul style="list-style-type: none"> Due to coadministration with ritonavir, there may be a risk of developing resistance to HIV protease inhibitors in people with uncontrolled or undiagnosed HIV-1 infection.
Remdesivir (VEKLURY)⁶	<ul style="list-style-type: none"> Avoid co-administration with chloroquine or hydroxychloroquine due to risk of reduced antiviral activity. 	<ul style="list-style-type: none"> Increased risk of transaminase elevations. 	N/A

Abbreviations: HIV = Human Immunodeficiency Virus; N/A = Not Applicable

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to September Week 4 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 04, 2023

1	COVID-19/ or SARS-CoV-2/ or COVID-19 Drug Treatment/	247189
2	molnupiravir.mp.	421
3	remdesivir.mp.	2492
4	Ritonavir/ or nirmatrelvir.mp.	5572
5	2 or 3 or 4	8009
6	1 and 5	3306
7	limit 6 to (english language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	365

Appendix 3: Key Inclusion Criteria

Population	Patients with mild-to-moderate COVID-19
Intervention	Molnupiravir, nirmatrelvir/ritonavir, and remdesivir
Comparator	Placebo or standard of care
Outcomes	Hospitalization or mortality
Timing	Within 5 to 7 days of symptom onset, depending on antiviral selection
Setting	Outpatients