Clinical Infectious Diseases

SPECIAL SECTION/INVITED ARTICLE

Molnupiravir and Nirmatrelvir-Ritonavir: Oral Coronavirus Disease 2019 Antiviral Drugs

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At a crucial time with rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant globally, the United States Food and Drug Administration has issued an emergency use authorization for 2 oral antivirals, molnupiravir (in persons aged ≥18 years) and nirmatrelvir-ritonavir (Paxlovid) (in persons aged ≥12 years weighing ≥40 kg), for the outpatient treatment of patients with mild to moderate coronavirus disease 2019 (COVID–19) who are at risk for progression. Molnupiravir is a nucleoside analogue, whereas nirmatrelvir is a SARS-CoV-2 main protease inhibitor, and ritonavir is a human immunodeficiency virus type 1 protease inhibitor. Drug interactions are a major concern for nirmatrelvir-ritonavir. Nirmatrelvir-ritonavir demonstrated a greater risk reduction in hospitalization and death than molnupiravir compared to placebo. Both drugs need to be started within 5 days of symptoms onset and given for 5 days' duration. This article reviews the 2 oral COVID-19 antiviral drugs including the mechanisms of action, antiviral activity, pharmacokinetics, drug interactions, clinical experience including trials, adverse events, recommended indications, and formulary considerations.

Keywords. COVID-19; nirmatrelvir; molnupiravir; Paxlovid; ritonavir.

The only antiviral agent against coronavirus disease 2019 (COVID-19) approved to date has been remdesivir, an intravenous nucleotide prodrug that binds to viral RNA–dependent RNA polymerase and inhibits viral replication. This drug, which received an emergency use authorization (EUA), was shown to be superior to placebo in shortening the time to recovery in hospitalized adults with evidence of lower respiratory tract infection and requiring supplemental oxygenation. Thus, there is a need for other antiviral drugs to treat earlier stages of disease in order to prevent hospitalization and death related to disease progression.

The United States (US) Food and Drug Administration (FDA) issued an EUA for the emergency use of the unproven products molnupiravir and nirmatrelvir-ritonavir (Paxlovid) [1–4]. Both agents are for the treatment of mild to moderate COVID-19 in adults and in pediatric patients 12 years of age and older for Paxlovid and adults 18 and older for molnupiravir who are at risk for progression to severe COVID-19 including hospitalization or death.

This article will review the 2 oral COVID-19 antiviral drugs including the mechanisms of action, antiviral activity, pharmacokinetics, drug interactions, clinical experience, adverse events, indications, and formulary considerations.

MECHANISM OF ACTION

Molnupiravir

Molnupiravir is a prodrug with antiviral activity that is metabolized to the cytidine nucleoside analogue N-hydroxycytidine (NHC), which is taken up by cells and phosphorylated to form the active ribonucleoside triphosphate (NHC-TP) [5]. NHC-TP is incorporated into severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA by the viral RNA polymerase causing an accumulation of errors in the viral genome, thus inhibiting replication. This agent has a different mechanism of action than nirmatrelvir.

Nirmatrelvir-Ritonavir

Nirmatrelvir is a SARS-CoV-2 main protease inhibitor (Mpro), and ritonavir is a human immunodeficiency virus type 1 (HIV-1) protease inhibitor and cytochrome P450 (CYP) 3A inhibitor [6]. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 Mpro in a biochemical assay with a inhibition constant (Ki) value of 3.1 nM and an half maximal inhibitory concentration (IC_{50}) value of 19.2 nM. Ritonavir is an HIV-1 protease inhibitor that is administered to increase the level of nirmatrelvir and has no activity against SARS-CoV-2 Mpro.

Received 28 January 2022; editorial decision 25 February 2022; published online 4 March 2022.
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Clinical Infectious Diseases® 2023;76(1):165–71

https://doi.org/10.1093/cid/ciac180

ANTIVIRAL ACTIVITY AND RESISTANCE CONSIDERATIONS

Molnupiravir

NHC, the nucleoside analogue metabolite of molnupiravir, was active in the cell culture assays against SARS-CoV-2 with a 50% effective concentration (EC_{50}) ranging between 0.67 and 2.66 μM. NHC had similar activity against the variants including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) [2]. When NHC was combined with remdesivir in cell culture assays, there was no evidence of antagonism. No data are currently available for activity against Omicron variants in cell cultures. Molnupiravir's active analogue has been shown to inhibit a range of viruses including chikungunya virus, Venezuelan equine encephalitis virus, respiratory syncytial virus, norovirus, influenza A and B viruses, Ebola virus, and human coronaviruses [7].

There have been no amino acid substitutions in SARS-CoV-2 associated with resistance to NHC in the phase 2 clinical trials of molnupiravir performed [2]. Following the 30 passages in cell culture, only a 2-fold decrease in the susceptibility was observed. NHC also demonstrated good activity in cell culture against the virus with polymerase substitutions associated with decreased remdesivir sensitivity, indicating a lack of cross-resistance [1].

Nirmatrelvir-Ritonavir

Nirmatrelvir exhibits antiviral activity in vitro against SARS-CoV-2 and cell culture activity against the Alpha, Beta, Gamma, Delta, and Lambda variants. It has shown activity against SARS-CoV-2 in A549-ACE2 cells with an EC_{50} of 77.9 and a 90% effective concentration of 215 nM [6, 8]. No data are currently available for activity against Omicron variants in cell cultures. However, nirmatrelvir has shown activity against Omicron in a biochemical assay [6]. It also has activity against other coronaviruses, including severe acute respiratory syndrome and Middle East respiratory syndrome [4].

There are limited SARS-CoV-2 sequencing data to characterize strains in clinical trials. Cross-resistance would not be expected between nirmatrelvir, molnupiravir, monoclonal antibodies, or remdesivir based upon different mechanisms of action.

PHARMACOKINETICS

Molnupiravir

Molnupiravir is available for oral use only in 200-mg capsules. The dose authorized is 800 mg (4 capsules) every 12 hours with or without food for 5 days. Repeat or extended courses of therapy are disallowed under the EUA. If a patient is late taking their dose, they can take it as soon as remembered if within 10 hours from when due (and resume normal dosing schedule); otherwise, they shall wait to take the next dose and not double up [1].

No dose adjustments are recommended for geriatric patients based on similar NHC pharmacokinetic data. Molnupiravir has not been assessed for use in children or adolescents and is not allowed under the EUA. NHC was not significantly eliminated by renal clearance when evaluated in mild to moderate renal impairment. Renal failure and dialysis are not expected to have a significant impact on NHC exposure, and no renal dose adjustments are recommended [1]. Preclinical data suggest that hepatic elimination is not a major route of elimination for NHC, and no dose adjustments are recommended for liver dysfunction [1].

NHC is cleared via metabolism to cytidine and/or uridine through pyrimidine metabolic pathways. Mean pharmacokinetics of NHC show an area under the curve (AUC) from 0 to 12 hours of 8260 ng × hour/mL, maximum serum concentration (C_{max}) 2330 ng/mL, Time to peak drug concentration (T_{max}) 1.5 hours, 35% reduced C_{max} with food but no change in AUC, plasma protein binding 0%, volume of distribution (Vd) 142 L, and half life (t1/2) 3.3 hours [1].

Nirmatrelvir-Ritonavir

Nirmatrelvir-ritonavir is available for oral use only, co-packaged as 150-mg and 100-mg tablets, respectively. The dose authorized is 300 mg/100 mg (2 nirmatrelvir tablets and 1 ritonavir tablet) every 12 hours with or without food for 5 days. Repeat or extended courses of therapy are disallowed under the EUA. If a patient is late taking their dose, they can take it as soon as remembered if within 8 hours from when due (and resume normal dosing schedule); otherwise, they shall wait to take the next dose and not double up [3].

Although no dose adjustment is needed for mild renal impairment (estimated glomerular filtration rate [eGFR] 60–89 mL/minute), nirmatrelvir dose is decreased to 150 mg and ritonavir remains at 100 mg every 12 hours for moderate impairment (eGFR 30–59 mL/minute). Due to a lack of data on appropriate dosing, nirmatrelvir-ritonavir is not recommended in severe renal impairment (eGFR <30 mL/minute). Dose adjustment is not necessary for mild to moderate hepatic impairment (Child-Pugh class A and B); however, nirmatrelvir-ritonavir is not recommended for use in severe impairment (Child-Pugh class C) due to limited safety/pharmacokinetic information [3].

Nirmatrelvir is a CYP3A4 substrate but has minimal metabolism and is eliminated via the renal route when given with the CYP3A4 inhibitor ritonavir. Mean pharmacokinetics of nirmatrelvir show an AUC_{inf} 23.01 μg × hour/mL, C_{max} 2.21 μg/mL, T_{max} 3 hours, 15% increased C_{max} with food but no change in AUC, plasma protein binding 69%, Vd 104.7 L, and $t_{1/2}$ 6.05 hours [3].

DRUG INTERACTIONS

Molnupiravir

No clinical drug interaction trials have been conducted with molnupiravir and concomitant medications; however, it has been shown that molnupiravir and NHC are not substrates, inhibitors,

or inducers of a variety of CYP enzymes, human P glycoprotein (P-gp), or assessed transport proteins. Therefore, no drug interactions have yet been identified with molnupiravir [1].

Nirmatrelvir-Ritonavir

Nirmatrelvir is a substrate and potential inhibitor for P-gp and CYP3A4 enzymes. Ritonavir is a substrate and inhibitor primarily for CYP3A4 but also CYP2D6. Ritonavir induces CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2B6 and other enzymes such as glucuronosyltransferase. Ritonavir provides boosting to ensure sufficient levels of nirmatrelvir and is required for the latter's use [3].

Coadministration with highly dependent substrates listed above in which significantly altered drug concentrations due to nirmatrelvir-ritonavir can result in serious or life-threatening reactions are contraindicated. This is also the case for potent CYP inducers, which may decrease nirmatrelvir-ritonavir, resulting in loss of virologic response and possible development of resistance [3]. Many of these medications are listed in Table 1, in which an alternative COVID-19 treatment or switch/discontinuation of the concomitant medication is recommended [9, 10]. Note that this list is not exhaustive, and prior to prescribing nirmatrelvir-ritonavir, every provider should thoroughly review their patient's list of concomitant medications, including over-the-counter medications and herbal supplements, to ensure that alternative therapies, dose adjustments, or increased monitoring is not needed. Warfarin levels may increase or decrease a mild to moderate degree necessitating monitoring while on nirmatrelvir-ritonavir therapy [10]. One free, comprehensive drug interaction resource available is COVID-19 Drug Interactions by the University of Liverpool (https://www.covid19-druginteractions.org/).

CLINICAL STUDIES

Molnupiravir

ClinicalTrials.gov NCT04405570 is a phase 2a trial evaluating the safety, tolerability, and antiviral efficacy of molnupiravir in the treatment of COVID-19. Among 202 treated participants, virus isolation was significantly lower in participants receiving 800 mg molnupiravir (1.9%) vs placebo (16.7%) at day 3 ($P = .02$). At day 5, virus was not isolated from any participants receiving 400 or 800 mg molnupiravir vs 11.1% of those receiving placebo ($P = .03$) [5].

Molnupiravir in outpatients (MOve-OUT) (NCT04575597) is a phase 2/3, double-blind, parallel-group, randomized, trial in at-risk, nonhospitalized symptomatic adults (≥18 years) with COVID-19 symptom onset of ≤5 days with a laboratory-confirmed diagnosis of SARS-CoV-2 infection. A total of 1433 subjects were randomized to receive either study drug or placebo. The number of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs 9.7% [68 of 699]; absolute difference, −3.0% [95% confidence interval {CI}, −5.9% to .1%]). Adjusted relative risk reduction of molnupiravir compared to placebo for all randomized subjects was 30% (95% CI: 1%–51%). One death was reported in the molnupiravir group (0.1%) and 9 deaths in the placebo group (1.3%), a risk of death that was lower by 89% (95% CI: 14%–99%) with molnupiravir than with placebo (Table 2). The 3 most common SARS-CoV-2 variants were B.1.617.2 (Delta; 58.1%), B.1.621 (Mu; 20.5%), and P.1 (Gamma; 10.7%). The molnupiravir group was associated with declines in SARS-CoV-2 RNA levels in nasopharyngeal swab samples at day 3 and day 5, with differences relative to placebo treatment in median SARS-CoV-2 declines from baseline of approximately

Table 1. Medications Generally Not Recommended for Coadministration With Nirmatrelvir-Ritonavir

Medication			
Alfuzosin	Diazepam	Lovastatin	Rivaroxaban
Aliskiren	Disopyramide	Lumateperone	Rosuvastatin
Alprazolam	Dofetilide	Lurasidone	Salmeterol
Amiodarone	Domperidone	Meperidine	Sildenafil
Apalutamide	Dronedarone	Mexiletine	Silodosin
Apixaban	Elbasvir-grazoprevir	Midazolam (oral)	Simvastatin
Atorvastatin	Eplerenone	Oxycodone	Sirolimus
Avanafil	Ergot derivatives	Phenobarbital	St John's wort
Bosentan	Estazolam	Phenytoin	Suvorexant
Carbamazepine	Everolimus	Pimozide	Tacrolimus
Cisapride	Fentanyl	Piroxicam	Tadalafil
Clonazepam	Flecainide	Primidone	Tamsulosin
Clopidogrel	Flibanserin	Propafenone	Ticagrelor
Clorazepate	Flurazepam	Quetiapine	Tramadol
Clozapine	Glecaprevir- pibrentasvir	Quinidine	Triazolam
Codeine	Hydrocodone	Ranolazine	Vorapaxar
Colchicine (with renal/ hepatic impairment)	Ivabradine	Rifampin	Vardenafil
Cyclosporine	Lomitapide	Rifapentine	

Table 2. Molnupiravir and Nirmatrelvir-Ritonavir in Clinical Trials

Study Design	Methods	Results	Interpretation
MOVe-OUT (NCT04575597): Phase 3, randomized,double-blind, placebo-controlled	Inclusion criteria: • Age ≥18 y • Laboratory-confirmed SARS-CoV-2 infection • Symptom onset within 5 d of randomization • ≥1 risk factor for severe COVID-19[a] • Not vaccinated against SARS-CoV-2 Exclusion criteria: • Anticipated hospitalization for COVID-19 within the next 48 h • Dialysis or estimated glomerular filtration rate <30 mL/min/1.73 m^2 • Pregnancy • Unwillingness to use contraception during the intervention period and for at least 4 d after completion of the regimen • Severe neutropenia (absolute neutrophil count of <500 cells/mL) • Platelet count <100 000/μL • SARS-CoV-2 vaccination Interventions: • Molnupiravir 800 mg or placebo orally twice daily for 5 d Primary endpoint: • COVID-19–related hospitalization or death through day 29	Participant characteristics: • Molnupiravir (n = 709), placebo (n = 699) Primary outcomes: • COVID-19–related hospitalizations or all-cause deaths by day 29: 6.8% (48 of 709) in molnupiravir group vs 9.7% (68 of 699) in placebo (hazard ratio, 0.69 [95% CI: .48–1.01]) • 29-d all-cause mortality: 1 (0.1%) death with molnupiravir and 9 (1.3%) deaths in the placebo group	• Relative risk reduction with molnupiravir: 30% • Absolute risk reduction: 2.9% • Number needed to treat: 35
EPIC-HR (NCT04960202): Phase 2/3, randomized, double-blind, placebo-controlled	Inclusion criteria: • Age ≥18 y • Laboratory-confirmed SARS-CoV-2 infection • Symptom onset within 5 d of randomization • ≥1 risk factor for severe COVID-19[b] • Not vaccinated against SARS-CoV-2 Exclusion criteria: • History of prior COVID-19 infection • SARS-CoV-2 vaccination Interventions: • Nirmatrelvir-ritonavir 300 mg/100 mg or placebo orally twice a day for 5 d Primary endpoint: • COVID-19–related hospitalization or death through day 28	Participant characteristics: • Nirmatrelvir-ritonavir (n = 1039), placebo (n = 1046) Primary outcomes[c]: • mITT analysis: 0.72% (5 of 697) in nirmatrelvir-ritonavir vs 6.45% (44 of 682) in placebo (risk reduction, –5.81% [95% CI: –7.78% to –3.84%]) • mITT1 analysis: 0.8% (8 of 1039) in nirmatrelvir-ritonavir vs 6.3% (66 of 1046) in placebo (risk reduction, –5.62% [95% CI: –7.21% to –4.03%]) • 28-day all-cause mortality: 0 (0 of 1039) deaths with nirmatrelvir-ritonavir and 1.1% (12 of 1046) in the placebo group	• Relative risk reduction with nirmatrelvir-ritonavir: 88% • Absolute risk reduction: 5.5% • Number needed to treat: 19

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; EPIC-HR, xxx; mITT, modified intention-to-treat; MOVe-OUT, xxx; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Risk factors for progression to severe disease: age ≥60 years, diabetes, obesity (body mass index [BMI] ≥30 kg/m^2), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer.

[b]Risk factors for progression to severe disease: age ≥60 years, diabetes, overweight (BMI ≥25 kg/m^2), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, or medically related technological dependence.

[c]The mITT analysis set included all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment; the mITT1 analysis set included all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.

0.2 $\log_{10}$ copies/mL and approximately 0.5 $\log_{10}$ copies/mL, respectively ($P < .05$) [1, 2, 11].

Nirmatrelvir-Ritonavir

Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) (NCT04960202) is a phase 2/3, randomized, double-blind, placebo-controlled study in at-risk nonhospitalized symptomatic adults (≥18 years) with a laboratory-confirmed diagnosis of SARS-CoV-2 infection. A total of 2246 subjects were randomized to receive either study drug or placebo. The relative risk reduction of hospitalization or all-cause death at day 28 for nirmatrelvir-ritonavir compared to placebo was 88% (95% CI: 75%,94%: 8 of 1039 [0.8%] vs 66 of 1046 [6.3%]) . No death was reported in the nirmatrelvir-ritonavir group (0/1039) but 12 were reported in the placebo group (12/1046) through day 28 (Table 2). The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I. Relative to placebo,

nirmatrelvir-ritonavir treatment was associated with an approximately 0.9 $\log_{10}$ copies/mL greater decline in viral RNA levels in nasopharyngeal samples through day 5 [3, 4].

ADVERSE REACTIONS

Molnupiravir

The safety of molnupiravir was evaluated based on an analysis of a phase 3 double-blind trial (MOVe-OUT) in which 1411 nonhospitalized subjects with COVID-19 were randomized and treated with molnupiravir (n = 710) or placebo (n = 701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation. The most common adverse reactions in the molnupiravir treatment group were diarrhea (2%) nausea (1%), and dizziness (1%), which was equal in both the groups. Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a similar rate across both the groups (<2%). Most serious events were COVID-19 related in 7% of subjects receiving molnupiravir and 10% receiving placebo. Death occurred in 2 (<1%) of the subjects receiving molnupiravir and 12 (2%) of subjects receiving placebo. Discontinuation of study due to an adverse event occurred in 1% of subjects receiving molnupiravir and 3% receiving placebo [1, 2, 11].

Nirmatrelvir-Ritonavir

The safety of nirmatrelvir-ritonavir is based on data from EPIC-HR, a phase 2/3 randomized, placebo-controlled trial in nonhospitalized patients at high risk of developing severe COVID-19. A total of 2224 symptomatic adult subjects received at least 1 dose of either nirmatrelvir-ritonavir (n = 1109) or placebo (n = 1115). Adverse events were those reported while subjects were on study medication and through day 34 after initiating study treatment. The nirmatrelvir/ritonavir group had higher adverse events (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group, which were dysgeusia (6% and <1%), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%). The proportions of subjects who discontinued treatment due to an adverse event were 2% in the nirmatrelvir-ritonavir group and 4% in the placebo group [3, 4].

INDICATIONS

Eligibility and prescribing requirements for the use of both the oral antivirals molnupiravir and nirmatrelvir-ritonavir are currently under EUA by the FDA for the outpatient treatment of mild to moderate COVID-19. Prescribers must adhere to the requirements specified in the applicable FDA Fact Sheet for Healthcare Providers and by the state requirements. The National Institutes of Health (NIH) COVID-19 treatment guidelines have proposed a prioritization scheme for when there are supply constraints [9]. Each of the oral therapies has potential advantages and disadvantages, which are summarized in Table 3 [1–4, 11]. Molnupiravir has relatively lower efficacy and has not been evaluated in transplant recipients. In addition, due to significant drug interactions and the difficulty with outpatient therapeutic drug monitoring, nirmatrelvir-ritonavir will be challenging to use in most transplant recipients with COVID-19. This may also be enhanced by the theoretical concern of mutagenicity for the virus in the immunocompromised patients. Thus, since neither drug has been studied among compromised hosts, to prevent progression in transplant recipients, sotrovimab or intravenous remdesivir may be preferable as first-line outpatient therapy [12].

Molnupiravir

Molnupiravir is authorized for outpatient treatment of mild to moderate COVID-19 in adults (≥18 years) initiated as soon as possible and within 5 days of symptom onset. Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment may complete the full 5-day treatment course per the healthcare provider's discretion.

As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in vivo rodent mutagenicity assays. One study produced results that were equivocal; in the other study there was no evidence for mutagenicity.

Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes; therefore, molnupiravir is not recommended for use during pregnancy. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

Molnupiravir is not authorized for use in patients <18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity were observed in rats after repeated dosing [1, 2].

Nirmatrelvir-Ritonavir

Nirmatrelvir-ritonavir (Paxlovid) is given orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset. Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment may complete the full 5-day treatment course per the healthcare provider's discretion.

Table 3. Comparison of Molnupiravir and Nirmatrelvir-Ritonavir for At-Risk Patients With Mild to Moderate Coronavirus Disease 2019

Clinical Parameters	Molnupiravir	Nirmatrelvir-Ritonavir
Indication	• ≥18 y: At-risk patients with mild to moderate COVID-19 within 5 d of symptom onset	• ≥12 y (≥40 kg): At-risk patients with mild to moderate COVID-19 within 5 d of symptom onset
Dose and duration	• 800 mg (four 200-mg capsules) taken orally every 12 h for 5 d with or without food	• 300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100-mg tablet), every 12 h for 5 d with or without food • Dose reduction for moderate renal impairment (eGFR 30–59 mL/min): 150 mg nirmatrelvir (one 150-mg tablet) with 100 mg ritonavir (one 100-mg tablet) every 12 h for 5 d
Adverse reactions	• Diarrhea, nausea, and dizziness	• Dysgeusia, diarrhea, hypertension, and myalgia
Precautions	• Not recommended for use during pregnancy • Not authorized for use in patients aged <18 y	• Hepatotoxicity reported rarely • Should be used with caution in pregnancy and only when mAb therapy is unavailable • Developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection (albeit, the risk of this is low)
Contraindications	• No contraindications based on the limited available under EUA	• Hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components • Coadministration with drugs highly dependent on CYP3A for clearance • Coadministration with potent CYP3A inducers resulting in significantly reduced nirmatrelvir or ritonavir plasma concentrations
Drug interactions	• No drug interactions have been identified based on limited data	• Extensive drug interactions that may preclude therapy or require therapy/dose modifications
Advantages	• Oral therapy • No drug interaction	• Oral therapy • Higher efficacy
Disadvantages	• Not recommended in pregnancy • Not recommended in patients aged <18 y • Lower efficacy	• Major drug interactions • Not recommended in patients with severe renal impairment (eGFR <30 mL/min) • Not recommend in patients with severe hepatic impairment (Child-Pugh class C)
Limitations of authorized use	• Not authorized for use in patients aged <18 y • Initiation of treatment in patients hospitalized due to COVID-19 • Longer than 5 consecutive days • Preexposure or postexposure prophylaxis	• Initiation of treatment in patients hospitalized due to COVID-19 • Longer than 5 consecutive days • Preexposure or postexposure prophylaxis

Abbreviations: COVID-19, coronavirus disease 2019; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; HIV, human immunodeficiency virus; mAb, monoclonal antibody.

Based on findings from animal reproduction studies, nirmatrelvir-ritonavir was not associated with fetal harm when administered to pregnant individuals. There are no available human data on the use of nirmatrelvir in pregnant individuals to evaluate the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes; however, ritonavir has not been identified in observational studies to be a risk factor for major birth defects.

The use in children as young as 12 years, who are at least 40 kg, has been included in nirmatrelvir-ritonavir's EUA largely based on expected similar levels to be obtained using adult dosing based on pharmacokinetic data. The safety and efficacy of nirmatrelvir-ritonavir have not been established in pediatric patients [3, 4].

FORMULARY CONSIDERATIONS

For the treatment of mild to moderate COVID-19, there are a variety of therapies (although limited monoclonal antibody options are active against the Omicron variant) for the clinician to consider, each with its own pros and cons. The challenge while the supplies of most treatments are limited will be ensuring both optimal (limiting to the highest risk based on vaccination status, immunocompromise, age, and comorbidities) and equitable access. Although some health systems have developed highly successful approaches for including disadvantaged communities with central determination and weighted lotteries with monoclonal antibodies, due to the current distribution of molnupiravir and nirmatrelvir-ritonavir to limited retail pharmacies, it will be hard to prevent solely first-come-first-serve access to these treatments [13].

Although there is currently no direct patient cost for molnupiravir or nirmatrelvir-ritonavir, as they are being supplied directly by the federal government, expenditures from the government estimate taxpayers are paying $706 or $530 per course, respectively [14, 15].

Based on the relative likelihood of each option preventing hospitalization and death and national guideline recommendations from the NIH, one may consider the approach shown in Figure 1 when determining which therapy to prescribe for high-risk outpatients with COVID-19 [9].

CONCLUSIONS

The FDA has issued an EUA for the emergency use of 2 new oral antiviral drugs, nirmatrelvir-ritonavir and molnupiravir,

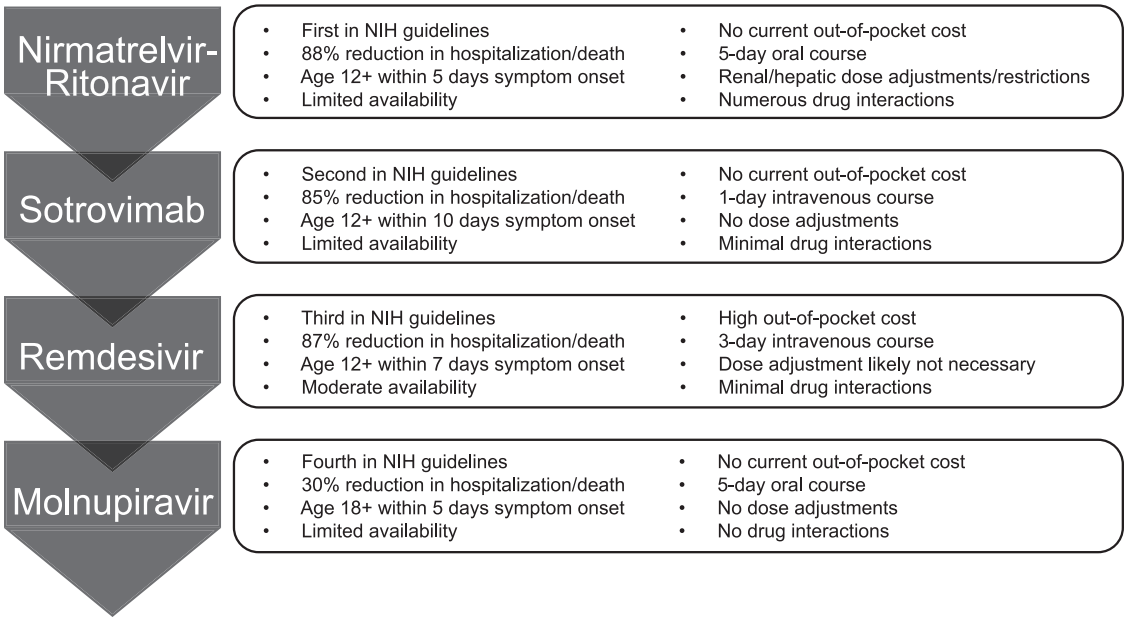

Figure 1. Therapy options for treatment of mild to moderate coronavirus disease 2019. These recommendations have not been established for the severely immunocompromised host or organ transplant recipients. Abbreviation: NIH, National Institutes of Health.

for the treatment of mild to moderate COVID-19. These 2 drugs differ in their mechanism of action. Drug interactions are a major concern for nirmatrelvir-ritonavir but not for molnupiravir. Although there is no head-to-head comparison performed to date, nirmatrelvir-ritonavir demonstrated a greater risk reduction in hospitalization and death compared to placebo than molnupiravir compared to placebo. Both drugs are well-tolerated but need to be started within 5 days of the onset of symptoms and given for 5 days' duration. Both nirmatrelvir-ritonavir and molnupiravir are important additions for the early treatment of COVID-19 as oral agents to reduce serious consequences of hospitalization and death during this pandemic.

Notes

Potential conflicts of interest. L. D. S. reports an unpaid leadership role or fiduciary role on the American College of Physicians Michigan Chapter Program Planning Committee and is chair of the Infectious Diseases Society of America Journal of Infectious Disease search committee. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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