Nirmatrelvir and Ritonavir (Systemic)

Antiviral; SARS-CoV-2 main protease (Mpro) inhibitor.

Class: 8:18.92 • Antivirals, Miscellaneous (AHFS primary)

Brands: Paxlovid®

Special Alerts:

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Uses

Coronavirus Disease 2019 (COVID-19)

- Nirmatrelvir with low-dose ritonavir (*ritonavir-boosted* nirmatrelvir) is available under an emergency use authorization (EUA) for the treatment of mild to moderate COVID-19 in adults and pediatric patients (≥12 years of age weighing ≥40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing who are at high risk of progression to severe COVID-19, including hospitalization or death.
- Consult nirmatrelvir EUA letter of authorization (https://www.fda.gov/media/155049/download), EUA fact sheet for healthcare providers (https://www.fda.gov/media/155050/download), and EUA fact sheet for patients, parents, and caregivers (https://www.fda.gov/media/155051/download) for additional information.
- *Ritonavir-boosted* nirmatrelvir is *not* authorized under the EUA for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19, for preexposure or postexposure prophylaxis of COVID-19, or for use >5 consecutive days.
- There are several therapeutic options available for treatment of nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression. When selecting an appropriate treatment, consider factors such as clinical efficacy and availability of the various options, feasibility of administering parenteral medications (i.e., remdesivir), potential for significant drug-drug interactions (e.g., those associated with the use of ritonavir-boosted nirmatrelvir), and regional prevalence of variants of concern.
- The National Institutes of Health (NIH) COVID-19 treatment guidelines panel recommends use of *ritonavir-boosted* nirmatrelvir or remdesivir, in order of preference, for treatment of nonhospitalized adult patients with COVID-19 who do not require hospitalization or supplemental oxygen but are at high risk for progression to severe disease. If *ritonavir-boosted* nirmatrelvir and remdesivir are unavailable, not feasible, or clinically inappropriate, the panel recommends bebtelovimab or molnupiravir, in no order of preference.
- The Infectious Diseases Society of American (IDSA) suggests a 5-day treatment course of *ritonavir-boosted* nirmatrelvir, dosed based on renal function, starting within 5 days of symptom onset over no *ritonavir-boosted* nirmatrelvir treatment in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease. Patients with mild to moderate COVID-19 who are hospitalized for reasons other than COVID-19 and who are at high risk of progression to severe disease may also receive *ritonavir-boosted* nirmatrelvir.
- Ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with other medications and may not be a safe choice for all patients. However, because the antiviral combination is the only highly effective oral option for treatment of COVID-19, the NIH guideline panel states that drug-drug interactions that can be safely managed should not preclude the use of this regimen.
- Consult the most recent guidelines available from NIH (https://www.covid19treatmentguidelines.nih.gov/) and IDSA (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) for additional information.
- Use of *ritonavir-boosted* nirmatrelvir early in the disease process when viral loads are high confers maximum benefit; therefore, it is critical to make a rapid diagnosis and treat nonhospitalized patients with COVID-19 early in the disease course.
- *Ritonavir-boosted* nirmatrelvir is expected to be active against all Omicron subvariants, although clinical efficacy data are lacking.
- Recent case reports suggest that some patients who have completed a 5-day course of *ritonavir-boosted* nirmatrelvir and have recovered can experience viral rebound (i.e., a recurrence of symptoms or a new positive viral test after having tested negative). There is currently no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound. Based on currently available data, CDC states that patient monitoring continues to be the most appropriate management for such patients.

Dosage and Administration

General

Pretreatment Screening

- Monitor baseline renal and liver function.

Dispensing and Administration Precautions

- *Ritonavir-boosted* nirmatrelvir is available in 2 packaging configurations: a dose pack that contains 300 mg nirmatrelvir and 100 mg ritonavir and a dose pack that contains 150 mg nirmatrelvir and 100 mg ritonavir. Healthcare providers should be aware of differences in the ritonavir tablet appearance, including shape, color, and debossing depending on the package provided to the patient. In patients with moderate renal impairment, only dispense the dose pack that contains 150 mg nirmatrelvir and 100 mg ritonavir. If this lower strength dose pack is unavailable for dispensing to patients with moderate renal impairment, pharmacists should refer to instructions in the document entitled "Important Paxlovid EUA dispensing information for patients with moderate renal impairment".
- Prescriptions must specify the numeric dose of each active ingredient in the antiviral drug combination (e.g., 300 mg nirmatrelvir with 100 mg ritonavir). Wrong-dose medication errors have occurred with *ritonavir-boosted* nirmatrelvir during prescribing, dispensing, and administration of the drug. Many of these errors have occurred during patient self-administration and generally involved patients taking the wrong combination of nirmatrelvir tablets and ritonavir tablets from the blister card. The blister card indicates which tablets need to be taken in the morning and evening each day.
- **Completion of FDA MedWatch forms to report all medication errors and all serious adverse events potentially related to ritonavir-boosted nirmatrelvir is mandatory.** The FDA fact sheet for health care providers should be consulted for requirements and instructions regarding reporting of adverse reactions and medication errors.

Other General Considerations

- Patients should continue isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Patients on ritonavir- or cobicistat-containing HIV or hepatitis C virus treatment regimens should continue their treatment as indicated. No dosage adjustment is required when *ritonavir-boosted* nirmatrelvir is coadministered with other products containing ritonavir or cobicistat.

Administration

Oral Administration

Administer orally without regard to food.

Swallow tablets whole; do not chew, break, or crush.

Must administer nirmatrelvir in conjunction with low-dose ritonavir at the same time twice daily. Ritonavir is a pharmacokinetic enhancer that improves the pharmacokinetic profile of nirmatrelvir.

Paxlovid® is available as a 5-day blister pack; each daily blister card contains a morning dose (one or two 150-mg nirmatrelvir tablets and one 100-mg ritonavir tablet) and evening dose (one or two 150-mg nirmatrelvir tablets and one 100-mg ritonavir tablet). (See Dispensing and Administration Precautions under Dosage and Administration.)

If a dose of *ritonavir-boosted* nirmatrelvir is missed by ≤8 hours, take the prescribed dose as soon as possible. If a dose is missed by >8 hours, administer prescribed dose at the next scheduled time; do not administer an additional dose to replace the missed dose.

Dosage

Pediatric Patients

Treatment of Mild to Moderate COVID-19 in Nonhospitalized Patients

Oral: ≥12 years of age weighing ≥40 kg: FDA EUA permits use of 300 mg of nirmatrelvir (two 150 mg tablets) orally twice daily in conjunction with 100 mg of ritonavir (one 100 mg tablet) orally twice daily for 5 days (*ritonavir-boosted* nirmatrelvir) for the treatment of mild to moderate COVID-19. Complete full 5-day treatment course.

Administer *ritonavir-boosted* nirmatrelvir as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.

If hospitalization occurs due to progression to severe or critical COVID-19 after initiation of *ritonavir-boosted* nirmatrelvir therapy, treatment course may be continued per the clinician's discretion.

Adults

Treatment of Mild to Moderate COVID-19 in Nonhospitalized Patients

Oral: EUA permits use of 300 mg of nirmatrelvir (two 150 mg tablets) orally twice daily in conjunction with 100 mg of ritonavir (one 100 mg tablet) orally twice daily for 5 days (*ritonavir-boosted* nirmatrelvir) for the treatment of mild to moderate COVID-19. Complete full 5-day treatment course.

Administer *ritonavir-boosted* nirmatrelvir as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.

If hospitalization occurs due to progression to severe or critical COVID-19 after initiation of *ritonavir-boosted* nirmatrelvir therapy, treatment course may be continued per the clinician's discretion.

Special Populations

Hepatic Impairment

Mild or moderate hepatic impairment (Child-Pugh class A or B): No dosage adjustment of *ritonavir-boosted* nirmatrelvir necessary.

Severe hepatic impairment (Child-Pugh class C): Pharmacokinetic profile and safety of *ritonavir-boosted* nirmatrelvir not established; *ritonavir-boosted* nirmatrelvir not recommended in such patients.

Renal Impairment

Moderate renal impairment (eGFR 30 to <60 mL/minute): Reduce nirmatrelvir dosage to 150 mg twice daily in conjunction with ritonavir 100 mg twice daily for 5 days. Prescribing clinicians must specify the numeric dose of nirmatrelvir and ritonavir (e.g., 150 mg nirmatrelvir with 100 mg ritonavir for patients with moderate renal impairment) on prescriptions and should counsel patients about renal dosing instructions. When dispensing ritonavir-boosted nirmatrelvir for patients with moderate renal impairment, only dispense the dose pack that contains 150 mg nirmatrelvir and 100 mg ritonavir. If this lower strength dose pack is unavailable for dispensing to patients with moderate renal impairment, the pharmacist should refer the document entitled "Important Paxlovid EUA dispensing information for patients with moderate renal impairment".

Mild renal impairment (eGFR 60 to <90 mL/minute): No dosage adjustment necessary.

Severe renal impairment (eGFR <30 mL/minute): Appropriate dosage not established; use not recommended in such patients.

Geriatric Patients

No specific dosage recommendations.

Cautions

Contraindications

- History of clinically significant hypersensitivity reactions to any ingredient in the preparation.
- Concomitant use of drugs that are highly dependent on cytochrome P-450 (CYP) isoenzyme 3A for metabolism and for which elevated plasma concentrations are associated with serious and/or life-threatening events (e.g., alfuzosin, ranolazine, amiodarone, dronedarone, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine, dihydroergotamine, ergotamine, methylergonovine, lovastatin, simvastatin, sildenafil [Revatio®] for treatment of pulmonary arterial hypertension, triazolam, oral midazolam).
- Concomitant use of potent CYP3A inducers that can reduce nirmatrelvir or ritonavir plasma concentrations and result in possible loss of virologic response and resistance (e.g., apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort [*Hypericum perforatum*]).

Warnings/Precautions

Serious Adverse Reactions Due to Drug Interactions

Must be used in conjunction with ritonavir. Failure to administer nirmatrelvir with the recommended dosage of ritonavir will result in subtherapeutic nirmatrelvir concentrations and inadequate virologic response. Consider the cautions, precautions, contraindications, and drug interactions associated nirmatrelvir and ritonavir.

Concomitant use of *ritonavir-boosted* nirmatrelvir with certain drugs is contraindicated or requires particular caution. Concomitant use with some drugs may result in clinically important adverse effects, including severe, life-threatening, or fatal events, due to higher exposures of the concomitant drug or higher exposures of nirmatrelvir and/or ritonavir. Concomitant use with other drugs may result in drug interactions leading to loss of therapeutic effect of *ritonavir-boosted* nirmatrelvir and possible development of viral resistance. Because nirmatrelvir and ritonavir are inhibitors of CYP3A, concomitant use with drugs metabolized by CYP3A may increase plasma concentrations of CYP3A substrate drugs.

Allergic Reactions/Hypersensitivity

Hypersensitivity (i.e., angioedema, hives, mild skin eruptions, pruritus) reported in patients receiving ritonavir-boosted nirmatrelvir. Anaphylaxis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome reported in patients receiving ritonavir.

Immediately discontinue treatment if signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis develop and initiate appropriate treatment and/or supportive care.

Hepatotoxicity

Hepatotoxicity (i.e., elevations in serum aminotransferase concentrations, clinical hepatitis, jaundice) reported in patients receiving ritonavir.

Use ritonavir with caution in patients with preexisting liver disease, liver enzyme abnormalities, or hepatitis.

HIV-1 Resistance Development

Because nirmatrelvir is coadministered with ritonavir, cross-resistance to HIV protease inhibitors (HIV PIs) may occur in individuals with uncontrolled or undiagnosed HIV-1 infection.

EUA Requirements for Patient Monitoring and Mandatory FDA MedWatch Reporting

Safety and efficacy of *ritonavir-boosted* nirmatrelvir not established. FDA EUA that permits use of *ritonavir-boosted* nirmatrelvir for the treatment of mild to moderate COVID-19 in certain adults and pediatric patients requires use of dosages recommended in the EUA.

Only limited data available to date regarding adverse effects associated with *ritonavir-boosted* nirmatrelvir. Serious and unexpected adverse events may occur that have not been previously reported with use of the drugs together.

Completion of FDA MedWatch forms to report all medication errors and all serious adverse events potentially related to ritonavir-boosted nirmatrelvir is mandatory. Consult the FDA fact sheet for health care providers for requirements and instructions regarding reporting of adverse reactions and medication errors.

Specific Populations

Pregnancy

Nirmatrelvir: Data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Reduced fetal body weight observed in animal studies

Ritonavir: Published observational studies have not identified an increase in the risk of major birth defects when ritonavir was used in pregnant women. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage.

Estimated background risk of major birth defects and miscarriage in the indicated population unknown. COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Lactation

Nirmatrelvir: Not known whether nirmatrelvir is distributed into human or animal milk or has effects on the breast-fed infant or milk production.

Ritonavir: Limited published data indicate that ritonavir is present in human milk. Not known whether ritonavir has effects on the breast-fed infant or milk production.

Consider developmental and health benefits of breast-feeding along with the mother's clinical need for *ritonavir-boosted* nirmatrelvir and any potential adverse effects on the breast-fed child from the drug or from the underlying maternal condition.

Females with COVID-19 who are breast-feeding should follow clinical guidelines to avoid exposing the infant to the virus.

Females and Males of Reproductive Potential

Use of ritonavir may reduce efficacy of combined hormonal contraceptives; advise patients to use an effective alternative contraceptive method or an additional barrier method of contraception until completion of one additional menstrual cycle.

Pediatric Use

The FDA EUA permits use of *ritonavir-boosted* nirmatrelvir for the treatment of COVID-19 in certain pediatric patients ≥12 years of age weighing ≥40 kg. Use of *ritonavir-boosted* nirmatrelvir is not authorized for pediatric patients <12 years of age or those weighing <40 kg.

Safety and efficacy of *ritonavir-boosted* nirmatrelvir not established in pediatric patients.

Pharmacokinetics of *ritonavir-boosted* nirmatrelvir not evaluated in pediatric patients <18 years of age. EUA-recommended dosage of *ritonavir-boosted* nirmatrelvir is expected to result in plasma concentrations of the drugs in patients ≥12 years of age weighing ≥40 kg that are comparable to those observed in adults.

Geriatric Use

In the EPIC-HR clinical trial, 13% of individuals who received *ritonavir-boosted* nirmatrelvir were ≥65 years of age and 3% were ≥75 years of age.

Hepatic Impairment

Moderate hepatic impairment: Systemic exposure to nirmatrelvir not substantially altered following administration of *ritonavir-boosted* nirmatrelvir.

Severe hepatic impairment: *Ritonavir-boosted* nirmatrelvir not studied.

Renal Impairment

Mild renal impairment (eGFR 60 to <90 mL/minute): Peak plasma concentrations or systemic exposure of nirmatrelvir increase by 30 or 24%, respectively, following administration of *ritonavir-boosted* nirmatrelvir.

Moderate renal impairment (eGFR 30 to <60 mL/minute): Peak plasma concentrations or systemic exposure of nirmatrelvir increase by 38 or 87%, respectively, following administration of *ritonavir-boosted* nirmatrelvir.

Severe renal impairment (eGFR <30 mL/minute): Peak plasma concentrations or systemic exposure of nirmatrelvir increase by 48 or 204%, respectively, following administration of *ritonavir-boosted* nirmatrelvir.

Common Adverse Effects

Dysgeusia, diarrhea, hypertension, myalgia.

Interactions

Nirmatrelvir must be used with a pharmacokinetic enhancer (i.e., low-dose ritonavir); consider drug interactions associated with both nirmatrelvir and ritonavir.

Nirmatrelvir: In vitro, nirmatrelvir is a substrate of P-glycoprotein (P-gp) and CYP3A4, but not a substrate of BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, or OATPs 1B1, 1B3, 2B1, and 4C1. Does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Nirmatrelvir has potential to reversibly and time-dependently inhibit CYP3A4 and P-gp. Does not induce CYP isoenzymes at clinically relevant concentrations.

Ritonavir: In vitro, ritonavir is primarily a substrate of CYP3A, and appears to be a substrate of CYP2D6. Ritonavir is an inhibitor of CYP3A and to a lesser extent CYP2D6. Appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

The following drug interactions are based on studies using *ritonavir-boosted* nirmatrelvir. Guidelines from the National Institutes of Health (NIH) state that because *ritonavir-boosted* nirmatrelvir is the only highly effective oral option for treatment of COVID-19, drug-drug interactions that can be safely managed should not preclude the use of this regimen; consult the most recent version of the NIH COVID-19 guideline (https://www.covid19treatmentguidelines.nih.gov/) for specific recommendations regarding safety of coadministration of specific drugs with *ritonavir-boosted* nirmatrelvir.

Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes

CYP3A Inducers: Potential pharmacokinetic interaction with drugs that induce CYP3A (decreased plasma concentrations of nirmatrelvir and ritonavir which may lead to reduced virologic response).

Substrates of CYP3A

Substrates of CYP3A: Potential pharmacokinetic interaction with drugs principally metabolized by CYP3A (increased plasma concentrations of drug metabolized by CYP3A). Concomitant use of nirmatrelvir and ritonavir with drugs highly dependent on CYP3A for metabolism and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Concomitant use of nirmatrelvir and ritonavir with other CYP3A substrates may require dosage adjustment or additional monitoring.

Specific Drugs

Drug	Interaction	Comments
Alfuzosin	Possible increased alfuzosin concentrations and increased risk of serious and/or life-threatening reactions (e.g., hypotension)	Concomitant use contraindicated
Antiarrhythmic agents (amiodarone, bepridil, dronedarone, flecainide, systemic lidocaine, propafenone, quinidine)	Possible increased antiarrhythmic agent concentrations	Amiodarone, dronedarone, flecainide, propafenone, quinidine: Concomitant use contraindicated Bepridil, systemic lidocaine: Use with caution; monitor therapeutic concentrations, if available
Anticoagulants, oral (rivaroxaban, warfarin, dabigatran)	Dabigatran: Possible increased dabigatran concentrations and increased risk of bleeding Rivaroxaban: Possible increased rivaroxaban concentrations and increased risk of bleeding Warfarin: Possible altered warfarin concentrations	Dabigatran: Depending on indication and renal function, reduce dosage of dabigatran or avoid concomitant use Rivaroxaban: Avoid concomitant use Warfarin: Closely monitor INR if concomitant use with *ritonavir-boosted* nirmatrelvir is necessary
Anticonvulsants (carbamazepine, phenobarbital, phenytoin)	Carbamazepine: Possible decreased systemic exposure to nirmatrelvir and ritonavir, loss of virologic response, and development of nirmatrelvir resistance; possible increased carbamazepine concentrations Phenobarbital, phenytoin: Decreased systemic exposure to nirmatrelvir and ritonavir, loss of virologic response, and development of nirmatrelvir resistance; possible decreased phenobarbital or phenytoin concentrations	Concomitant use contraindicated; do not initiate *ritonavir-boosted* nirmatrelvir immediately after discontinuation of carbamazepine, phenobarbital, or phenytoin due to delayed offset of these drugs
Antifungals, azoles (isavuconazonium, itraconazole, ketoconazole, voriconazole)	Isavuconazonium (prodrug of isavuconazole): Possible increased isavuconazole concentrations and increased nirmatrelvir and ritonavir concentrations Itraconazole: Possible increased itraconazole concentrations and increased nirmatrelvir and ritonavir concentrations Ketoconazole: Possible increased ketoconazole concentrations and increased nirmatrelvir and ritonavir concentrations Voriconazole: Possible decreased voriconazole concentrations and increased nirmatrelvir and ritonavir concentrations	Voriconazole: Avoid concomitant use
Antimycobacterials (bedaquiline, rifabutin, rifampin)	Bedaquiline: Possible increased bedaquiline concentrations Rifabutin: Increased rifabutin concentrations Rifampin: Substantially decreased nirmatrelvir concentrations and possible loss of virologic response and development of resistance	Rifampin: Concomitant use contraindicated; consider alternative antimycobacterial (e.g., rifabutin); do not initiate *ritonavir-boosted* nirmatrelvir immediately after discontinuation of rifampin due to delayed offset of rifampin

Antineoplastic agents (apalutamide, abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine)	Apalutamide: Possible decreased systemic exposure to nirmatrelvir and ritonavir, loss of virologic response, and development of nirmatrelvir resistance Ibrutinib, neratinib, venetoclax: Possible increased antineoplastic concentrations Encorafenib, ivosidenib: Possible increased antineoplastic concentrations and potential for serious and/or life-threatening adverse effects (e.g., QT interval prolongation) Vincristine, vinblastine: Possible increased antineoplastic concentrations and potential for clinically important hematologic or GI adverse effects	Apalutamide: Concomitant use contraindicated; do not initiate ritonavir-boosted nirmatrelvir immediately after discontinuation of apalutamide due to delayed offset of apalutamide Encorafenib, ibrutinib, ivosidenib, neratinib, venetoclax: Avoid concomitant use
Antipsychotics (clozapine, lurasidone, pimozide, quetiapine)	Potential for serious and/or life-threatening adverse effects (e.g., arrhythmia)	Clozapine, lurasidone, pimozide: Concomitant use contraindicated Quetiapine: If concomitant use with *ritonavir-boosted* nirmatrelvir is necessary, reduce quetiapine dosage and monitor for quetiapine adverse effects
Antiretroviral agents, HIV protease inhibitors (PIs) (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir)	Possible increased systemic exposure to the HIV PI	In patients currently receiving a *ritonavir- or cobicistat- boosted* HIV regimen, continue treatment as indicated and monitor for increased ritonavir or nirmatrelvir adverse events
Benzodiazepines (midazolam, triazolam)	Oral midazolam or triazolam: Possible increased midazolam or triazolam concentrations and potential for serious and/or life-threatening effects (e.g., prolonged or increased sedation or respiratory depression) Parenteral midazolam: Possible increased midazolam concentrations	Oral midazolam or triazolam: Concomitant use contraindicated Parenteral midazolam: Use concomitantly with caution and in monitored setting where respiratory depression and/or prolonged sedation can be managed; consider reduced midazolam dosage, especially if multiple midazolam doses are given
Bictegravir	Fixed combination of bictegravir, emtricitabine, and tenofovir alafenamide fumarate (BIC/FTC/TAF): Possible increased bictegravir concentrations	
Bosentan	Possible increased bosentan concentrations	Discontinue bosentan for ≥36 hours prior to initiating *ritonavir-boosted* nirmatrelvir
Bupropion	Possible decreased concentrations of bupropion and its active metabolite (hydroxybupropion)	Monitor for adequate clinical response to bupropion
Calcium-channel blocking agents (amlodipine, diltiazem, felodipine, nicardipine, nifedipine)	Possible increased concentrations of the calcium-channel blocking agent	Use concomitantly with caution; clinical monitoring recommended If concomitant use cannot be avoided, dosage reduction of calcium-blocking agent may be necessary
Colchicine	Possible increased colchicine concentrations and potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment	Concomitant use contraindicated
Corticosteroids (betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone)	Possible increased corticosteroid concentrations and increased risk of adrenal insufficiency or Cushing's syndrome	Consider alternative corticosteroid (e.g., beclomethasone, prednisolone)
Dasabuvir	Possible increased HCV antiviral drug concentrations if used with fixed combination ombitasvir/paritaprevir/ritonavir/dasabuvir	In patients currently receiving a *ritonavir-boosted* HCV antiviral regimen, continue treatment as indicated and monitor for increased adverse effects of *ritonavir-boosted* nirmatrelvir or the HCV antiviral drug
Delavirdine	Possible pharmacokinetic interaction	
Didanosine	Possible increased didanosine concentrations	
Digoxin	Possible increased digoxin concentrations	Use concomitantly with caution; monitor digoxin concentrations and adjust dosage as clinically indicated
Efavirenz	Possible increased efavirenz plasma concentrations	
Elbasvir	Possible increased elbasvir concentrations and substantially increased grazoprevir concentrations if *ritonavir-boosted* nirmatrelvir used with fixed combination elbasvir/grazoprevir; increased grazoprevir concentrations may increase risk	

	of increased ALT concentrations	
Emtricitabine	No effect on emtricitabine exposures if used with fixed combination of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF)	
Ergot alkaloids (dihydroergotamine, ergotamine, methylergonovine)	Potential for serious or life-threatening adverse effects (e.g., vasospasm, ischemia of extremities or other tissues)	Concomitant use contraindicated
Estrogens	Oral hormonal contraceptives containing ethinyl estradiol: Possible decreased ethinyl estradiol concentrations	Use additional nonhormonal contraception methods during the 5 days of treatment and until 1 menstrual cycle after discontinuance of *ritonavir-boosted* nirmatrelvir
Fentanyl	Possible increased fentanyl concentrations	Carefully monitor patient for fentanyl therapeutic and adverse effects, including potentially fatal respiratory depression
Glecaprevir and pibrentasvir	Increased HCV antiviral drug concentrations if *ritonavir-boosted* nirmatrelvir is used with fixed combination glecaprevir/pibrentasvir	Concomitant use not recommended
Grazoprevir	Increased elbasvir concentrations and substantially increased grazoprevir concentrations if *ritonavir-boosted* nirmatrelvir is used with fixed combination elbasvir/grazoprevir; increased grazoprevir concentrations may increase risk of increased ALT concentrations	
HMG-CoA reductase inhibitors (statins)	Lovastatin, simvastatin: Possible increased antilipemic concentrations and increased risk of statin-associated adverse effects, including myopathy and rhabdomyolysis Atorvastatin, rosuvastatin: Possible increased antilipemic concentrations and increased risk of statin-associated adverse effects	Atorvastatin, rosuvastatin: Consider temporarily withholding atorvastatin and rosuvastatin during *ritonavir-boosted* nirmatrelvir therapy; atorvastatin and rosuvastatin do not need to be held prior to or after discontinuance of ritonavir-boosted nirmatrelvir Lovastatin, simvastatin: Concomitant use with *ritonavir-boosted* nirmatrelvir contraindicated; discontinue lovastatin and simvastatin at least 12 hours prior to initiation of *ritonavir-boosted* nirmatrelvir, during the 5 days of treatment, and for 5 days after completion of *ritonavir-boosted* nirmatrelvir therapy
Immunosuppressive agents (cyclosporine, sirolimus, tacrolimus)	Cyclosporine, sirolimus, tacrolimus: Possible increased immunosuppressive agent concentrations	Cyclosporine, tacrolimus: Monitor plasma concentrations of immunosuppressive agent; avoid concomitant use if monitoring of immunosuppressive agent concentrations not feasible Sirolimus: Avoid concomitant use
Macrolides (clarithromycin, erythromycin)	Possible increased macrolide concentration	
Maraviroc	Possible increased maraviroc concentrations	
Meperidine	Possible increased meperidine concentrations and increased risk of serious respiratory depression or hematologic abnormalities	Concomitant use contraindicated
Methadone	Possible decreased methadone concentrations	Closely monitor for opiate withdrawal since some patients may need adjustment of methadone maintenance dosage
Nevirapine	Potential pharmacokinetic interaction	
Ombitasvir	Increased HCV antiviral drug concentrations if *ritonavir-boosted* nirmatrelvir is used with fixed combination ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir/dasabuvir	In patients currently receiving a *ritonavir-boosted* HCV antiviral regimen, continue treatment as indicated and monitor for increased adverse effects of *ritonavir-boosted* nirmatrelvir or HCV antiviral drug
Paritaprevir	Possible increased HCV antiviral drug concentrations if used with fixed combination ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir/dasabuvir	In patients currently receiving a *ritonavir-boosted* HCV antiviral regimen, continue treatment as indicated and monitor for increased adverse effects of *ritonavir-boosted* nirmatrelvir or HCV antiviral drug
Raltegravir	Possible decreased plasma concentrations of raltegravir	
Ranolazine	Possible increased ranolazine concentrations and increased risk of serious and/or life-threatening adverse effects	Concomitant use contraindicated

St. John's wort *(Hypericum perforatum)*	Possible decreased nirmatrelvir and ritonavir concentrations, and possible loss of virologic response and development of resistance	Concomitant use contraindicated; do not initiate *ritonavir-boosted* nirmatrelvir immediately after discontinuation of St. John's wort due to delayed offset of St. John's wort
Salmeterol	Possible increased salmeterol concentrations and increased risk of QT interval prolongation, palpitations, and sinus tachycardia	*Ritonavir-boosted* nirmatrelvir: Concomitant use not recommended
Sildenafil	Possible increased sildenafil concentrations and increased risk of sildenafil-associated adverse effects (e.g., hypotension, visual disturbances, prolonged erection, syncope)	Sildenafil (Revatio®) for treatment of pulmonary arterial hypertension (PAH): Concomitant use with *ritonavir-boosted* nirmatrelvir contraindicated
Sofosbuvir	Possible increased sofosbuvir/velpatasvir/voxilaprevir concentrations if *ritonavir-boosted* nirmatrelvir is used with fixed combination of sofosbuvir, velpatasvir, and voxilaprevir (sofosbuvir/velpatasvir/voxilaprevir)	
Tenofovir alafenamide	Fixed combination of bictegravir, emtricitabine, and tenofovir alafenamide fumarate (BIC/FTC/TAF): Possible increased TAF concentrations if used with *ritonavir-boosted* nirmatrelvir	
Trazodone	Possible increased trazodone concentrations and increased risk of nausea, dizziness, hypotension, syncope	Consider reduced trazodone dosage
Velpatasvir	Possible increased sofosbuvir/velpatasvir/voxilaprevir concentrations if *ritonavir-boosted* nirmatrelvir is used with fixed combination of sofosbuvir, velpatasvir, and voxilaprevir (sofosbuvir/velpatasvir/voxilaprevir)	
Voxilaprevir	Possible increased sofosbuvir/velpatasvir/voxilaprevir concentrations if *ritonavir-boosted* nirmatrelvir is used with fixed combination of sofosbuvir, velpatasvir, and voxilaprevir (sofosbuvir/velpatasvir/voxilaprevir)	
Zidovudine	Possible decreased plasma concentrations of zidovudine	

Pharmacokinetics

Absorption

Bioavailability

Following oral administration of *ritonavir-boosted* nirmatrelvir, systemic exposure of nirmatrelvir increases in a less than dose proportional manner up to 750 mg (single dose) and up to 500 mg twice daily. Following administration of *ritonavir-boosted* nirmatrelvir twice daily for 10 days, steady-state concentrations of nirmatrelvir are attained on day 2 with approximately 2-fold accumulation.

Following oral administration of a single 300-mg dose of nirmatrelvir with 100 mg of ritonavir in healthy individuals, peak plasma concentrations of nirmatrelvir and ritonavir are achieved in 3 and 3.98 hours, respectively.

Food

Following coadministration of a suspension formulation of nirmatrelvir and ritonavir tablets with a high fat meal, mean peak plasma concentrations increased by approximately 15% and mean AUC increased by 1.6% relative to administration in a fasted state.

Distribution

Extent

Nirmatrelvir: Not known whether nirmatrelvir is distributed into human or animal milk.

Ritonavir: Limited published data indicate that ritonavir is present in human milk.

Plasma Protein Binding

Nirmatrelvir or ritonavir is 69 or 98–99% bound to plasma proteins, respectively.

Elimination

Metabolism

Nirmatrelvir is a CYP3A4 substrate but metabolic clearance is minimal when coadministered with ritonavir. Ritonavir is primarily metabolized by CYP3A4 and, by a lesser extent, CYP2D6.

Elimination Route

Following oral administration of a radiolabeled dose of nirmatrelvir suspension and ritonavir, 49.6% of the nirmatrelvir dose recovered in urine and 35.3% of the dose recovered in feces.

Half-Life

Nirmatrelvir: Following a single 300-mg dose of nirmatrelvir administered in conjunction with 100 mg of ritonavir, mean elimination half-life of nirmatrelvir is 6.05 hours in healthy individuals.

Ritonavir: Following a single 300-mg dose of nirmatrelvir administered in conjunction with 100 mg of ritonavir, mean elimination half-life of nirmatrelvir is 6.15 hours in healthy individuals.

Specific Populations

Effects of age and sex on the pharmacokinetics of *ritonavir-boosted* nirmatrelvir not established.

Pharmacokinetics of *ritonavir-boosted* nirmatrelvir not evaluated in pediatric patients.

Based on adults with similar body weight to pediatric patients weighing ≥40 kg in the EPIC-HR clinical trial, the EUA-recommended dosage of *ritonavir-boosted* nirmatrelvir is expected to result in plasma concentrations in patients ≥12 years of age weighing ≥40 kg that are comparable to those observed in adults.

Systemic exposure is decreased in Japanese individuals compared with individuals from Western countries; however, the difference is not clinically significant.

Stability

Storage

Oral

Tablets

Blister packs containing nirmatrelvir and ritonavir tablets: 20–25°C (excursions permitted between 15–30ºC).

Actions

- Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro) (also referred to as 3C-like protease [3CLpro] or nsp5 protease).
- Following binding of nirmatrelvir directly to the SARS-CoV-2 Mpro active site, inhibition of SARS-CoV-2 Mpro prevents viral replication.

- Nirmatrelvir had similar cell culture antiviral activity (EC50 values 3-fold or less relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1621), and Omicron (B.1.1.529/BA.1) variants.
- Among patients included in the EPIC-HR trial with available sequence analysis data, the following treatment-emergent SARS-CoV-2 Mpro substitutions were detected more commonly among patients treated with *ritonavir-boosted* nirmatrelvir: A7S/T/V, L30F, M82I/R, G109E/R/V, P132L/S, C145F/R/Y, D153H/Y, E166V, T196A/K/M/R, W207L/S/del, A260D/T/V, D263E, A266P/V, and V297A/F/del. The following Mpro ORFlab cleavage site substitutions were also detected: Q5324H/R, A5328P/S, and T6449I/P. None of these substitutions occurred in patients treated with *ritonavir-boosted* nirmatrelvir who were also hospitalized; clinical significance of these substitutions is not known.
- Limited SARS-CoV-2 sequencing data are available to characterize nirmatrelvir resistance in clinical trials. The SARS-CoV-2 Mpro substitutions A260V or A260T emerged in 4% (4/97) of patients receiving *ritonavir-boosted* nirmatrelvir in the EPIC-HR clinical trial with available sequence analysis data.
- Cross-resistance not expected between nirmatrelvir and anti-SARS-CoV-2 monoclonal antibodies or remdesivir.

Advice to Patients

- The Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization (EUA) of Paxlovid for the Treatment of Coronavirus Disease 2019 (COVID-19) must be provided to patients or parent/caregivers prior to administration of *ritonavir-boosted* nirmatrelvir.
- Inform patients to take ritonavir-boosted nirmatrelvir with or without food as instructed. Advise patients to swallow tablets whole and not to chew, break, or crush the tablets. Advise the patient of the importance of completing the full 5-day treatment course. If the patient misses a dose within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.
- Inform patients that hypersensitivity reactions have been reported, even following a single dose of ritonavir-boosted nirmatrelvir. Advise them to discontinue the drug and to inform their healthcare provider at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- To ensure appropriate dosing in patients with moderate renal impairment, instruct such patients that they will be taking one 150 mg nirmatrelvir tablet with one 100 mg ritonavir tablet together twice daily for 5 days. In the event that the 150 mg/100 mg dose pack is unavailable, the pharmacist should refer to the provided instructions entitled “Important Paxlovid EUA dispensing information for patients with moderate renal impairment” for dispensing of ritonavir-boosted nirmatrelvir to patients with moderate renal impairment and patients should be informed that their daily blister card has been altered to ensure they receive the correct dose.
- Inform patients or parent/caregivers that FDA authorized the emergency use of nirmatrelvir, which is an investigational drug that has not received FDA approval, for use in certain adults and pediatric patients with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.
- Inform patients or parent/caregivers about the significant known and potential risks and benefits of *ritonavir-boosted* nirmatrelvir, and the extent to which such risks and benefits are unknown.
- Advise females of reproductive potential that ritonavir may decrease the effectiveness of hormonal contraceptives and that an effective alternative contraceptive method or an additional barrier method should be used during treatment.
- Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and herbal supplements, as well as any concomitant illnesses.
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.
- Advise patients of other important precautionary information. (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Nirmatrelvir is not commercially available. FDA issued an emergency use authorization (EUA) for *ritonavir-boosted* nirmatrelvir that allows use of the drug for the treatment of mild to moderate COVID-19 in certain adults and pediatric patients who are at high risk for progression to severe COVID-19, including hospitalization or death. The manufacturer (Pfizer) should be contacted for information on how to obtain *ritonavir-boosted* nirmatrelvir for use under the EUA.

Nirmatrelvir with Ritonavir

Oral

Kit

Nirmatrelvir with Ritonavir

150 mg nirmatrelvir; 100 mg ritonavir dose pack Each blister card contains 4 tablets: 2 tablets, nirmatrelvir 150 mg 2 tablets, ritonavir 100 mg	**Paxlovid™** (each carton contains 20 tablets divided in 5 blister cards), Pfizer
300 mg nirmatrelvir; 100 mg ritonavir dose pack Each blister card contains 6 tablets: 4 tablets, nirmatrelvir 150 mg 2 tablets, ritonavir 100 mg	**Paxlovid™** (each carton contains 30 tablets divided in 5 blister cards), Pfizer