Nirmatrelvir and Ritonavir
(Systemic)

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

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

Brands: Paxlovid®

Special Alerts:

The American Society of Health-System Pharmacists, Inc. represents that the information provided in the accompanying monograph was formulated with a reasonable standard of care, and in conformity with professional standards in the field. Readers are cautioned that a combined regimen of ritonavir-boosted nirmatrelvir is not an approved treatment for coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, but rather, is being investigated for and is currently available under an FDA emergency use authorization (EUA) for the treatment of mild to moderate COVID-19 in certain nonhospitalized patients. The American Society of Health-System Pharmacists, Inc. makes no representations or warranties express or implied, including, but not limited to, any implied warranty of merchantability and/or fitness for a particular purpose, with respect to the information contained in the accompanying monograph, and specifically disclaims all such warranties. Readers of this information are advised that ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information contained in the monograph in any and all practice settings. Readers are advised that decisions regarding drug therapy are complex medical decisions requiring the use of the information contained in the monograph for any errors or omissions, and/or for any consequences arising from the use of the information contained in the monograph in any and all practice settings. Readers are advised that decisions regarding drug therapy are complex medical decisions requiring the use of the information contained in the monograph for any errors or omissions, and/or for any consequences arising from the use of the information contained in the monograph in any and all practice settings. Readers are advised that decisions regarding drug therapy are complex medical decisions requiring the use of the information contained in the monograph for any errors or omissions, and/or for any consequences arising from the use of the information contained in the monograph in any and all practice settings.

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 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 America (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.

Dosage

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 nirmatrelvir 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., 500 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.

Doseage

Pediatric Patients

Treatment of Mild to Moderate COVID-19 in Nonhospitalized Patients

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nirmatrelvir and possible development of viral resistance. Because nirmatrelvir and ritonavir are
drugs may result in drug interactions leading to loss of therapeutic effect of concomitant drug or higher exposures of nirmatrelvir and/or ritonavir. Concomitant use with other interactions associated nirmatrelvir and ritonavir.

Warnings/Precautions

● 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, dronedare, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine, 

Hepatic 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.

Geriatic 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, dronedare, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine, dihydroergotamine, ergotamine, methylergonovine, lovastatin, simvastatin, sildenafil[Revatio]

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 nirmatrelvir 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.
Concomitant use of nirmatrelvir and ritonavir with other 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 can lead to decreased exposure of nirmatrelvir and ritonavir, which may result in reduced antiviral effectiveness. Therefore, coadministration of specific drugs with nirmatrelvir and ritonavir should be avoided.

**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 CYP3A, 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

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<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Alfuzosin</td>
<td>Possible increased alfuzosin concentrations and increased risk of serious and/or life-threatening reactions (e.g., hypotension)</td>
<td>Concomitant use contraindicated</td>
</tr>
<tr>
<td>Antiarrhythmic agents (amiodarone, bepridil, dronedarone, flecainide, systemic lidocaine, propafenone, quinidine)</td>
<td>Possible increased antiarrhythmic agent concentrations</td>
<td></td>
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<tr>
<td>Anticoagulants, oral (rivaroxaban, warfarin, dabigatran)</td>
<td>Dabigatran: Possible increased dabigatran concentrations and increased risk of bleeding</td>
<td>Rifapentin: Concomitant use contraindicated; consider alternative anticoagulant (e.g., warfarin); do not initiate ritonavir-boosted nirmatrelvir immediately after discontinuation of rifapentin due to delayed offset of rifapentin</td>
</tr>
<tr>
<td>Anticonvulsants (carbamazepine, phenobarbital, phenytoin)</td>
<td>Carbamazepine: Possible decreased systemic exposure to nirmatrelvir and ritonavir, loss of virologic response, and development of nirmatrelvir resistance; possible increased carbamazepine concentrations</td>
<td></td>
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<tr>
<td>Antifungals, azoles (isavuconazonium, itraconazole, ketoconazole, voriconazole)</td>
<td>Isavuconazonium (prodrug of isavuconazole): Possible increased isavuconazole concentrations and increased nirmatrelvir and ritonavir concentrations</td>
<td></td>
</tr>
<tr>
<td>Antimycobacterials (bedaquiline, rifabutin, rifampin)</td>
<td>Bedaquiline: Possible increased bedaquiline concentrations</td>
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Antineoplastic agents
(apalutamide, abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vinorelbine)

Bosentan: Possible increased bosentan concentrations for ≥36 hours prior to
Discontinue bosentan

Bictegravir: Fixed combination of bictegravir, emtricitabine, and tenofovir alafenamide fumarate (BIC/FTC/TAF): Possible increased bictegravir concentrations

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

Antipsychotics (clozapine, lurasidone, pimozide, quetiapine)

Antiretroviral agents, HIV protease inhibitors (PIs) (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir)

Antituberculosis agents (clarithromycin, rifampin, rifabutin)

Bupropion: Possible decreased concentrations of bupropion and its active metabolite

Calcium-channel blocking agents (amlodipine, diltiazem, felodipine, nicardipine, nifedipine)

Calcium-channel blockers: Avoid concomitant use

Corticosteroids (betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, mometasonolone, nivadipine, triamcinolone)

Corticosteroids: Concomitant use contraindicated

Dasabuvir: Possible increased HCV antiviral drug concentrations if used with fixed combination omibitasvir/paritaprevir/ritonavir/dasabuvir

Delavirdine: Possible pharmacokinetic interaction

Didanosine: Possible increased didanosine concentrations

Digoxin: Possible increased digoxin concentrations

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

Encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine: Use concomitantly with caution; monitor digoxin concentrations and adjust dosage as clinically indicated

Elbasvir: Monitor for adequate clinical response to elbasvir

Emtricitabine: Concomitant use contraindicated

Encorafenib, lurasidone, pimozide, quetiapine: Concomitant use contraindicated

Enfuvirtide: Avoid concomitant use

Fosamprenavir, inefuvirtide: Avoid concomitant use

FTC/TAF): Possible increased bictegravir concentrations and potential for serious and/or life-threatening adverse effects (e.g., QT interval prolongation)

Grazoprevir: Possible increased elbasvir concentrations

HIV PI inhibitors (PIs) (Saquinavir, tipranavir) possible increased elbasvir concentrations

Indinavir, nelfinavir, fosamprenavir, ritonavir, losartan, valsartan, olmesartan, irbesartan, aliskiren, losartan: Possible increased midazolam or triazolam concentrations and potential for serious and/or life-threatening adverse effects (e.g., QT interval prolongation, depression and/or arrhythmia)

Ibrutinib, neratinib: Possible increased antineoplastic concentrations and potential for serious and/or life-threatening adverse effects (e.g., QT interval prolongation)

Ivosidenib: Possible increased antineoplastic concentrations and potential for clinically important hematologic or GI adverse effects

Vincristine, vinblastine: Use concomitantly with caution; monitor for adequate clinical response to vincristine
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<tr>
<th><strong>Emtricitabine</strong></th>
<th><strong>Grazoprevir</strong></th>
<th><strong>Fentanyl</strong></th>
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<tbody>
<tr>
<td>No effect on emtricitabine exposures if used with fixed combination of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF)</td>
<td>Pibrentasvir</td>
<td>Carefully monitor patient for fentanyl therapeutic and adverse effects, including potentially fatal respiratory depression</td>
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<tr>
<th><strong>Ergot alkaloids</strong> <em>(dihydroergotamine, ergotamine, methylergonovine)</em></th>
<th><strong>Emtricitabine</strong></th>
<th><strong>Ergot alkaloids</strong></th>
</tr>
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<tbody>
<tr>
<td>Potential for serious or life-threatening adverse effects (e.g., vasospasm, ischemia of extremities or other tissues)</td>
<td>No effect on emtricitabine concentrations</td>
<td>Concomitant use contraindicated</td>
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<tr>
<th><strong>Estrogens</strong></th>
<th><strong>Ergot alkaloids</strong></th>
<th><strong>Emtricitabine</strong></th>
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<tr>
<td>Oral hormonal contraceptives containing ethinyl estradiol: Possible decreased ethinyl estradiol concentrations</td>
<td>Potential for serious or life-threatening adverse effects (e.g., vasospasm, ischemia of extremities or other tissues)</td>
<td>Use additional nonhormonal contraception methods during the 5 days of treatment and until 1 menstrual cycle after discontinuance of ritonavir-boosted nirmatrelvir</td>
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<tr>
<th><strong>Glecaprevir and pibrentasvir</strong></th>
<th><strong>Fentanyl</strong></th>
<th><strong>Glecaprevir</strong></th>
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<tr>
<td>Increased HCV antiviral drug concentrations if ritonavir-boosted nirmatrelvir is used with fixed combination glecaprevir/pibrentasvir</td>
<td>Possible increased fentanyl concentrations</td>
<td>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</td>
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<th><strong>HMG-CoA reductase inhibitors (statins)</strong></th>
<th><strong>Glecaprevir and pibrentasvir</strong></th>
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<tr>
<td>Lovastatin, simvastatin: Possible increased antilipemic concentrations and increased risk of statin-associated adverse effects</td>
<td>Increased HCV antiviral drug concentrations if ritonavir-boosted nirmatrelvir is used with fixed combination elbasvir/grazoprevir; increased grazoprevir concentrations may increase risk of increased ALT concentrations</td>
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<td>Lovastatin, simvastatin: Possible increased antilipemic concentrations and increased risk of statin-associated adverse effects</td>
<td>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</td>
<td>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</td>
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<td>Lovastatin, simvastatin: Concomitant use with ritonavir-boosted nirmatrelvir contraindicated; discontinue lovastatin and simvastatin at least 12 hours prior to initiation of ritonavir-boosted nirmatrelvir,</td>
<td>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</td>
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<th><strong>Immunosuppressive agents (cyclosporine, sirolimus, tacrolimus)</strong></th>
<th><strong>Macrolides</strong> <em>(clarithromycin, erythromycin)</em></th>
<th><strong>Maraviroc</strong></th>
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<tr>
<td>Cyclosporine, sirolimus, tacrolimus: Possible increased immunosuppressive agent concentrations</td>
<td>Possible increased macrolide concentration</td>
<td>Possible increased maraviroc concentrations</td>
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<th><strong>Macrolides</strong> <em>(clarithromycin, erythromycin)</em></th>
<th><strong>Maraviroc</strong></th>
<th><strong>Meperidine</strong></th>
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<tr>
<td>Possible increased macrolide concentration</td>
<td>Possible increased maraviroc concentrations</td>
<td>Possible increased meperidine concentrations and increased risk of serious respiratory depression or hematologic abnormalities</td>
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<th><strong>Meperidine</strong></th>
<th><strong>Methadone</strong></th>
<th><strong>Meropenem</strong></th>
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<tr>
<td>Possible increased meperidine concentrations and increased risk of serious respiratory depression or hematologic abnormalities</td>
<td>Possible decreased methadone concentrations</td>
<td>Concomitant use contraindicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Methadone</strong></th>
<th><strong>Meropenem</strong></th>
<th><strong>Nevirapine</strong></th>
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</thead>
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<tr>
<th><strong>Nevirapine</strong></th>
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<th><strong>Paritaprevir</strong></th>
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</thead>
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<td>Potential pharmacokinetic interaction</td>
<td>Increased HCV antiviral drug concentrations if ritonavir-boosted nirmatrelvir is used with fixed combination ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir/dasabuvir</td>
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<th><strong>Ombitasvir</strong></th>
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<tr>
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<th><strong>Ranazine</strong></th>
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<td>Possible increased ranazine concentrations and increased risk of serious and/or life-threatening adverse effects</td>
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<td>Possible increased ranazine concentrations and increased risk of serious and/or life-threatening adverse effects</td>
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### Pharmacokinetics

#### Absorption

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.

#### Bioavailability

- **Sildenafil (Revatio®)**: Concomitant use not recommended

#### 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

- **Nirmatrelvir or ritonavir**: 69 or 98-99% bound to plasma proteins, respectively.

#### Plasma Protein Binding

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

- **Nirmatrelvir**: Not known whether nirmatrelvir is distributed into human or animal milk.
- **Ritonavir**: Limited published data indicate that ritonavir is present in human milk.

#### 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


### Actions

- **Nirmatrelvir** is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro) (also referred to as 3C-like protease [3CLpro] or nspr5 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 ORF1ab cleavage site substitutions were also detected: Q532H/R, A5328P/S, and T6449I/U. 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 patients 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**

<table>
<thead>
<tr>
<th>Tablet Type</th>
<th>Dose</th>
<th>Paxlovid™ (each carton contains 30 tablets divided in 5 blister cards), Pfizer</th>
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</thead>
<tbody>
<tr>
<td>150 mg nirmatrelvir; 100 mg ritonavir dose pack</td>
<td>Each blister card contains 6 tablets: 2 tablets, nirmatrelvir 150 mg 2 tablets, ritonavir 100 mg</td>
<td></td>
</tr>
</tbody>
</table>

**Paxlovid™ (each carton contains 20 tablets divided in 5 blister cards), Pfizer**

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<tbody>
<tr>
<td>300 mg nirmatrelvir; 100 mg ritonavir dose pack</td>
<td>Each blister card contains 4 tablets: 2 tablets, nirmatrelvir 150 mg 2 tablets, ritonavir 100 mg</td>
<td></td>
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</tbody>
</table>