Consideration for the Initiation of Paxlovid™ (nirmatrelvir/ritonavir) in COVID-19

For patients (≥12 years old) with symptomatic mild-to-moderate COVID-19, **Paxlovid™** may be considered, as authorized by Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) 12/2021. The following are authorized use criteria as described by the EUA and are considerations for use of **Paxlovid™**. **However, specific high-risk criteria are not required for use and can be prescribed at physician discretion.**

I. **Patient/disease-specific considerations for greatest benefit**

a. ≤5 days from initial symptom onset
b. Age ≥18 years (or ≥12 years old and weight ≥40kg)
c. Weight ≥40kg
d. High risk for progressing to severe COVID-19 and/or hospitalization:
***Additional high-risk conditions can be identified at the discretion of covering physician*

- BMI ≥25
- Chronic kidney disease
- Diabetes
- Age ≥65
- Pregnancy
- Cardiovascular disease
- Hypertension
- COPD
- Other chronic respiratory illness
- HIV infection with CD4 count ≤200
- Solid organ or stem cell transplant
- Sickle cell disease
- Chemotherapy in the past year
- Immunosuppressant use for autoimmune disease
- Prednisone ≥20 mg/day (or equivalent) for ≥14 days
- Neurodevelopmental disorder
- Medical-related technological dependence (ex: trach, PEG)

II. **Dose/Administration:**

a. **Standard dosing**: 300mg nirmatrelvir (two 150mg tablets) + 100mg ritonavir (one 100mg tablets) with all three tablets taken together twice daily for 5 days
b. **Dose reduction for eGFR (≥30 to <60mL/min):** 150mg nirmatrelvir (one 150mg tablet) + 100mg ritonavir (one 100mg tablet) with both tablets taken together twice daily for 5 days
c. **Not recommended:** patients with severe renal impairment (eGFR <30mL/min) or patients with severe hepatic impairment (Child-Pugh Class C)

III. **Adverse Effects and Precautions:**

a. Common adverse events including diarrhea (6%), dysgeusia (3%), hypertension (1%) and myalgia (1%) have been observed in clinical trials.
b. Medication errors and/or serious adverse events should be reported to FDA MedWatch via the online website www.fda.gov/medwatch/report/htm or by calling 1-800-FDA-1088 to request a reporting form.

IV. **Contraindications:** Nirmatrelvir and ritonavir are both CYP3A4 substrates. Therefore the medication may be contraindicated with drugs highly dependent on the CYP3A4 pathway. Please see pages 3 & 4 for further details of interactions/contraindications.

a. **CYP3A4 Substrates**

Class	Medications
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin
Analgesics	Meperidine, propoxyphene
Antianginal	Ranolazine
Antiarrhythmic	Amiodarone, dronedarone, flecainide, propafenone, quinidine
Anti-gout	Colchicine
Antipsychotics	Lurasidone, pimozide, clozapine
Ergot derivatives	Dihydroergotamine, ergotamine, methylergonovine
HMG-CoA reductase inhibitors	Lovastatin, simvastatin
PDE-5 Inhibitor	Sildenafil (when used for pulmonary arterial hypertension)
Sedative/hypnotics	Triazolam, oral midazolam

b. **CYP3A4 Inducers**

Class	Medications
Anticancer drugs	Apalutamide
Anticonvulsant	Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	Rifampin
Herbal Products	St. John's Wort

V. **Other Drug Interactions/Mechanisms:**

a. It is strongly recommended that providers gather a medication history (both prescription and over the counter medications) prior to prescribing Paxlovid™.

b. Further information can be found on the following website. PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets) For HCPs (paxlovidhcp.com).

c. ***Please note this is not a comprehensive list and interactions for all medications should be assessed prior to prescribing nirmatrelvir/ritonavir****

Class	Medications
Antiarrhythmics	Bepridil, lidocaine (systemic)
Anticancer drugs	Abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine
Anticoagulants	Warfarin, rivaroxaban, dabigatran
Antidepressants	Bupropion, trazodone
Antifungals	Voriconazole, ketoconazole, isavuconazonium sulfate, itraconazole
Anti-HIV protease inhibitors	Amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir

Anti-HIV	Didanosine, delavirdine, efavirenz, maraviroc, nevirapine, raltegravir, zidovudine bictegravir/ emtricitabine/ tenofovir
Anti-infective	Clarithromycin, erythromycin
Antimycobacterial	Bedaquiline, rifabutin
Antipsychotics	Quetiapine
Calcium channel blockers	Amlodipine, diltiazem, felodipine, nicardipine, nifedipine
Cardiac glycosides	Digoxin
Endothelin receptor antagonists	Bosentan
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir ombitasvir/paritaprevir /ritonavir and dasabuvir sofosbuvir/velpatasvir/ voxilaprevir
HMG-CoA reductase inhibitors	Atorvastatin, rosuvastatin
Hormonal contraceptive	Ethinyl estradiol
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus
Long-acting beta-adrenoreceptor agonist	Salmeterol
Narcotic agents	Fentanyl, methadone
Sedative/hypnotics	IV midazolam
Systemic corticosteroids	Betamethasone, budesonide, ciclesonide, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone

Table 1: Contraindicated CYP3A4 Substrates:

Co-administration of Nirmatrelvir/ritonavir will lead to increased concentrations of medications listed:		
Class	**Medications**	**Effect of Co-administration**
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin	Co-administration contraindicated due to potential hypotension
Analgesics	Meperidine, propoxyphene	Co-administration contraindicated due to potential of serious respiratory depression or hematologic abnormalities
Antianginal	Ranolazine	Co-administration contraindicated due to potential for serious/life-threatening reactions
Antiarrhythmic	Amiodarone, dronedarone, flecainide, propafenone, quinidine	Co-administration contraindicated due to potential for cardiac arrhythmias
Anti-gout	Colchicine	Co-administration contraindicated due to potential for serious/life-threatening reactions in patients with renal and/or hepatic impairment
Antipsychotics	Lurasidone, pimozide, clozapine	Co-administration contraindicated due to serious/life-threatening reactions such as cardiac arrhythmias.
Ergot derivatives	Dihydroergotamine, ergotamine, methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized

		by vasospasm and ischemia of the extremities and other tissues including the central nervous system
HMG-CoA reductase inhibitors	Lovastatin, simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. *Discontinue lovastatin or simvastatin at least 12 hours prior to initiation of Paxlovid™, during treatment, and 5 days after completion of treatment
PDE-5 Inhibitor	Sildenafil (when used for pulmonary arterial hypertension)	Co-administration contraindicated due to potential for sildenafil associated adverse effects including visual abnormalities, hypotension, syncope, or prolonged erection
Sedative/hypnotics	Triazolam, oral midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression.

Table 2: Contraindicated CYP3A4 Inducers

Co-administration of medications listed will lead to decreased concentrations of nirmatrelvir/ritonavir		
Class	**Medications**	**Interaction**
Anticancer drugs	Apalutamide	Decreases nirmatrelvir/ritonavir concentrations. Co-administration contraindicated due to potential loss of virologic response/ possible resistance
Anticonvulsant	Carbamazepine, phenobarbital, phenytoin	Decreases nirmatrelvir/ritonavir concentrations. Co-administration contraindicated due to potential loss of virologic response/ possible resistance
Antimycobacterials	Rifampin	Decreases nirmatrelvir/ritonavir concentrations. Co-administration contraindicated due to potential loss of virologic response/ possible resistance
Herbal Products	St. John's Wort	Decreases nirmatrelvir/ritonavir concentrations. Co-administration contraindicated due to potential loss of virologic response/ possible resistance