SARS-CoV-2 THERAPEUTICS PROTOCOL
v1, 8/10/22

PURPOSE

This protocol specifies the criteria and procedures for pharmacists to initiate the dispensing of the oral SARS-CoV-2 therapeutic nirmatrelvir/ritonavir (Paxlovid) for the treatment of COVID-19 under the FDA's emergency use authorization.

CRITERIA

Pharmacists authorized to initiate the dispensing of oral Paxlovid according to the FDA's *Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid*[1].

Inclusion criteria (all of the following must be met):

- 12 years of age and older weighing at least 40 kilograms
- Positive results of direct SARS-CoV-2 viral testing within the past 5 days through any of the following:
    - Documentation of a polymerase chain reaction (PCR) test conducted off-site
    - Results from a CLIA-waived PCR test, nucleic acid amplification test (NAAT) or rapid antigen detection test (RADT) ordered and conducted onsite as authorized by this protocol
    - Self-report of a positive home test result from an RADT.

  Note: antibody tests are NOT considered to be direct SARS-CoV-2 tests
- At high risk for progression to severe COVID-19, including hospitalization or death[2]
- Sufficient information available to assess renal and hepatic function
- Sufficient information available to assess for potential drug interactions

Exclusion criteria (any one of the following are met):

- Severe renal impairment (eGFR <30 mL/min)
- Severe hepatic impairment (Child-Pugh Class C)
- History of clinically significant hypersensitivity reactions to nirmatrelvir, ritonavir or any other components
- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious or life-threatening reactions, including:
    - alfuzosin, silodosin
    - pethidine (meperidine)
    - ranolazine
    - amiodarone, dronedarone, flecainide, propafenone, quinidine
    - colchicine

[1] Available at: https://www.fda.gov/media/155050/download

[2] Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

  - lurasidone, pimozide, clozapine
  - eplerenone, ivabradine
  - dihydroergotamine, ergotamine, methylergonovine
  - lovastatin, simvastatin
  - voclosporin
  - lomitapide
  - eletriptan, ubrogepant
  - finerenone
  - naloxegol
  - sildenafil when used for pulmonary arterial hypertension (PAH)
  - triazolam, oral midazolam
  - flibanserin
  - tolvaptan
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance, including:
  - apalutamide
  - carbamazepine, phenobarbital, primidone, phenytoin
  - lumacaftor/ivacaftor
  - rifampin
  - St. John's Wort
- Co-administration with other medications for which dosage adjustment would be necessary due to a potential drug interaction (Appendix 1)
- Patients requiring hospitalization due to severe or critical COVID-19
- Desire for pre-exposure or post-exposure prophylaxis against COVID-19

MEDICATIONS

This protocol authorizes pharmacists to initiate the dispensing of:

Medication	Dose	SIG	Notes
nirmatrelvir/ritonavir (Paxlovid)	300 mg nirmatrelvir (two 150 mg tablets) co-packaged with 100 mg ritonavir	BID x 5 days	eGFR ≥60 mL/min
nirmatrelvir/ritonavir (Paxlovid)	150 mg nirmatrelvir co-packaged with 100 mg ritonavir	BID x 5 days	eGFR ≥30 to <60 mL/min

PROCEDURES FOR INITIATION AND MONITORING OF THERAPIES

Paxlovid therapy initiation and monitoring will be individualized based on patient history and consideration of contraindications and precautions of therapy as outlined in the FDA's *Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid*[3]. Pharmacists may utilize

[3] Available at: https://www.fda.gov/media/155050/download

the authority granted under this protocol to order and conduct CLIA-waived SARS CoV 2 testing.

Pharmacists must have sufficient information to determine eligibility to receive Paxlovid:

- A list of all patient medications, including over-the-counter medications to screen for drugs with potentially serious interactions with Paxlovid (Appendix 1)
- Electronic or printed health records less than 12 months old, including the most recent reports of laboratory blood work to review for kidney or liver problems; or
- Information received from a consult with the patient's health care provider

After assessment of information and determination of eligibility to receive Paxlovid under this protocol (**i.e. patient meets all inclusion criteria and has no exclusion criteria from above**), pharmacists are authorized to initiate the dispensing of Paxlovid as outlined in the Medication Table above.

EDUCATION REQUIREMENTS

Pharmacists must communicate to the patient and/or caregiver information consistent with the *"FACT SHEET FOR PATIENTS, PARENTS, and CAREGIVERS"*[4] and provide them with a copy prior to dispensing.

- Inform patients that hypersensitivity reactions have been reported, even after one dose
- Advise patients to discontinue the drug and inform their (Health Care Provider) HCP of the first sign of an allergic reaction
- Inform patients that Paxlovid may interact with some drugs and is contraindicated with some drugs
- Alert patients of the importance of completing the full 5-day treatment course
- Advise persons who are able to become pregnant of the need to abstain from sexual activity while taking Paxlovid or use a barrier method of contraception
- Inform patients about the possibility of "rebound COVID" after Paxlovid and steps they should take if this occurs[5]

DOCUMENTATION

Pharmacists will document via prescription record each person who receives Paxlovid under this protocol, including:

- Documentation of the assessment of renal and hepatic function, and patient medication list for contraindications and drug interactions
- Documentation as required in 201 KAR 2:170 for the dispensing of prescription medication
- Documentation that the individual receiving Paxlovid was provided with the required education pursuant to this protocol
- Documentation of mandatory reporting of any serious adverse events and medication

[4] Available at: https://www.fda.gov/media/155051/download

[5] Available at: https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_467.pdf

errors potentially related to PAXLOVID within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500[6]. Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

NOTIFICATION

Pharmacist(s) shall ask all persons receiving Paxlovid under this protocol for the name and contact information of the individual's primary care provider and shall provide notification of the medications dispensed under the protocol to the identified primary care provider within two (2) business days.

Any individual affirmatively stating that the individual does not have a primary care provider may still receive Paxlovid under this protocol provided all other applicable requirements of the protocol are met.

[If directed by the authorizing prescriber, the pharmacist(s) shall provide written notification via fax or other secure electronic means to the authorizing prescriber of persons receiving Paxlovid under this protocol within 7 days of initiating dispensing]

TERMS

This protocol is effective as of the date all parties execute the document. It shall remain in effect for a period of one year and shall automatically renew for successive one-year periods unless otherwise terminated by any party, with or without cause. Any termination without cause shall require prior notice to all parties of no less than sixty days.

[6] Available at: https://www.fda.gov/medwatch/report.htm

SIGNATURES

_____	_____
Prescriber Name	Date
_____	
Prescriber Signature	
_____	_____
Pharmacist Name	Date
_____	
Pharmacist Signature	

Appendix 1

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Analgesics	pethidine (meperidine)	↑ pethidine (meperidine)	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities *[see Contraindications (4)]*.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)].*
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor INR if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
Anticonvulsants	carbamazepine[a], phenobarbital, primidone, phenytoin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole,	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events *[see Dosage and Administration (2.4)]*.
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline rifabutin rifapentine	↑ bedaquiline ↑ rifabutin ↓ nirmatrelvir/ritonavir	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction. Avoid concomitant use with PAXLOVID.
Antipsychotics	lurasidone, pimozide, clozapine	↑ lurasidone ↑ pimozide ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension *[see Contraindications (4)]*.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Cardiovascular agents	eplerenone ivabradine	↑ eplerenone ↑ ivabradine	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia *[see Contraindications (4)]*. Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances *[see Contraindications (4)]*.
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar, clopidogrel	↑ aliskiren ↑ ticagrelor ↑ vorapaxar ↓ clopidogrel active metabolite	Avoid concomitant use with PAXLOVID.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Corticosteroids primarily metabolized by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)].*
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor elexacaftor/tezacaftor/ivacaftor tezacaftor/ivacaftor	↑ ivacaftor ↑elexacaftor/tezacaftor/ivacaftor ↑ tezacaftor/ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
Endothelin receptor antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ 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 *[see Contraindications (4)]*.
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir ombitasvir/paritaprevir/ritonavir and dasabuvir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID. Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	sofosbuvir/velpatasvir/ voxilaprevir		Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use *[see Dosage and Administration (2.4)]*.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	cyclosporine, tacrolimus	↑ cyclosporine ↑ tacrolimus	Avoid use of PAXLOVID when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions is recommended. Refer to the individual immunosuppressant product label for further information and obtain expert consultation from the patient's immunosuppressive therapy specialist.
	everolimus, sirolimus	↑ everolimus ↑ sirolimus	Avoid concomitant use of everolimus and sirolimus and PAXLOVID.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions *[see Contraindications (4)]*.
Migraine medications	eletriptan	↑ eletriptan	Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events *[see Contraindications (4)]*.
	ubrogepant	↑ ubrogepant	Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions *[see Contraindications (4)]*.
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia *[see Contraindications (4)]*.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Narcotic analgesics	fentanyl, hydrocodone, oxycodone	↑ fentanyl ↑ hydrocodone ↑ oxycodone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone or oxycodone is concomitantly administered with PAXLOVID.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use with PAXLOVID.
PDE5 inhibitor (when used for pulmonary arterial hypertension)	sildenafil (Revatio®)	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
	tadalafil (Adcirca®)	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID.
PDE5 inhibitor (when used for erectile dysfunction)	avanafil,	↑ avanafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil, ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil or avanafil with PAXLOVID. Refer to individual product label for more information.
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms *[see Contraindications (4)]*.
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.
Sedative/hypnotics	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered,

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression *[see Contraindications (4)]*.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia *[see Contraindications (4)]*.

a. See Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir (12.3).