Paxlovid

Antiviral for Severe Covid

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For the sake of simplicity, I will not comment on *molnupiravir*, the other antiviral being promoted under an EUA (Emergency Use Authorization), other than to tell you there are too many red flags about its safety and it doesn't appear to be as effective as Paxlovid, although there are no direct head-to-head trials. Teratogenicity (ability to cause birth defects/ fetal toxicity) and mutagenicity (the ability to cause tumors) are the chief concerns with molnupiravir.

With the direct antiviral nirmatrelvir/ritonavir (Paxlovid), we get a medicine that has also come to us via an EUA, which gives us reason to pause. In a 28-day study with over 1000 people at high risk of complicated covid in both the placebo arm and the treatment arm, Paxlovid decreased risk of hospitalization (6.3% placebo vs 0.8% Paxlovid) and risk of death (1.1% placebo vs 0% Paxlovid). This shows an exciting 85-90% reduction in hospitalization and 95-100% reduction in mortality among high-risk individuals (in the age of delta).

In the age of omicron, very few people will need drug intervention and I suspect this drug (which just became available) will make a bigger difference for coming variants. How this drug compares in safety with my current ivermectin and dexamethasone combination, of course, no one can accurately say. Furthermore, if someone takes Paxlovid, dexamethasone is considered relatively contraindicated, due to a potential drug interaction.

The following information is mostly cut and paste from the physician prescribing guidelines:

Dosage for Emergency Use of PAXLOVID: PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 Mpro in a biochemical assay with a Ki value of 3.1 nM and an IC50 value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 Mpro active site by X-ray crystallography.

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 Mpro. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

The dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. (30 pills total, nirmatrelvir #20, ritonavir #10)

PAXLOVID is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg.

Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

No dosage adjustment is needed in patients with mild renal impairment. In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dose of PAXLOVID to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID. Paxlovid is contraindicated in those with severe renal impairment (eGFR <30 mL/min)

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion. If the patient misses a dose of PAXLOVID 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 4 dose at the regularly scheduled time.

The patient should not double the dose to make up for a missed dose. PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken *with or without food* [see Clinical Pharmacology (12.3)]. The tablets should be swallowed whole and *not chewed, broken, or crushed*.

PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions [see Drug Interactions (7.3)]:

- Alpha1-adrenoreceptor antagonist: alfuzosin, tamsulosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anticoagulants; clopidogrel (Plavix), rivaroxaban (Xarelto)
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Contraceptives: may decrease efficacy
- Corticosteroids: *relatively contraindicated*
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin, (atorvastatin, rosuvastatin)
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

The following medicines are listed more alphabetically, for ease of reference:

• Amiodarone • Apalutamide • Bosentan • Carbamazepine	• Alfuzosin • Alprazolam • Atorvastatin • Avanafil

• Cisapride • Clopidogrel (Plavix) • Clozapine • Colchicine in patients with renal and/or hepatic impairment • Disopyramide • Dofetilide • Dronedarone • Eplerenone • Ergot derivatives • Flecainide • Flibanserin • Glecaprevir/pibrentasvir • Ivabradine • Lumateperone • Lurasidone • Mexiletine • Phenobarbital • Phenytoin • Pimozide • Propafenone • Quinidine • Ranolazine • Rifampin • Rifapentine • Rivaroxaban (Xarelto) • Sildenafil for pulmonary hypertension • St. John's wort • Tadalafil for pulmonary hypertension • Ticagrelor • Vorapaxar	• Clonazepam • Codeine • Cyclosporine[b] • Diazepam • Everolimus[b] • Fentanyl • Hydrocodone • Lomitapide • Lovastatin • Meperidine (pethidine) • Midazolam (oral) • Oxycodone • Piroxicam • Propoxyphene • Rosuvastatin • Salmeterol • Sildenafil for erectile dysfunction • Silodosin • Simvastatin • Sirolimus[b] • Suvorexant • Tacrolimus[b] • Tadalafil for erectile dysfunction • Tamsulosin • Tramadol • Triazolam • Varde

PAXLOVID is contraindicated with drugs that are 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.

PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer [see Drug Interactions (7.3)]:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (hypericum perforatum)

These strategies (discontinuation of contraindicated drugs) should be considered for the 5-day duration of ritonavir-boosted nirmatrelvir (Paxlovid) treatment and for at least 3 to 5 days after treatment completion.

The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group. Dysgeusia (bad taste in the mouth) 6%, was the only significant side effect.

So, in summation, we have an extremely well-tolerated, extremely efficacious antiviral with a whole lot of drug interactions for you and your provider to be aware of. Holding the listed drugs for 8 days total (5 days on medicine and 3 days after for clearance of Paxlovid) seems reasonable, until we know more. I, personally, prefer my ivermectin/dexamethasone combination as a first line therapy. We all know how difficult it can be to get ivermectin, however. Thusly I am thrilled to have an additional drug available and will be willing to prescribe it for anyone within 5 days of onset of covid symptoms.

Your Journey to Health and Healing,

Gary E Foresman MD