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# Paxlovid™ Information From FDA and Guidance for AES Members

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**Abstract**

This American Epilepsy Society (AES) official statement provides information and preliminary guidance to Society members related to the U.S. Food & Drug Administration (FDA) December 22, 2021 Emergency Use Authorization for Paxlovid™ for the oral treatment of mild to moderate COVID-19 in adults and children (≥12 years and weighing ≥40 kg). Paxlovid is likely to be widely prescribed, and important considerations for patients on antiseizure medications (ASMs) include key contraindications and potential toxicity or dose adjustments while taking Paxlovid. This statement highlights concerns and provides information about their pharmacologic basis. Of particular concern, concomitant use of Paxlovid with the ASMs carbamazepine, phenobarbital, phenytoin, and primidone is contraindicated, because they are strong inducers of the CYP3A4 isozyme that metabolizes Paxlovid and thereby could cause loss of virologic response and development of resistance. Alternate oral or intravenous COVID-19 treatments should be considered. A second concern is that Paxlovid may increase the plasma concentrations of many ASMs, because it inhibits the CYP3A4 isozyme. ASMs that are metabolized, at least in part, by CYP3A4 include cannabidiol, carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, everolimus, felbamate, lacosamide, midazolam, oxcarbazepine, perampanel, stiripentol, tiagabine, and zonisamide. Patients receiving these medications may warrant closer monitoring while being treated with Paxlovid.

**Keywords**

Paxlovid™, ritonavir, antiseizure medications, drug interactions, adverse effects, epilepsy, seizure, COVID-19

The American Epilepsy Society (AES) has compiled U.S. Food & Drug Administration (FDA) information and preliminary guidance for AES members on Paxlovid™, one of the new COVID-19 oral antivirals that is likely to be widely prescribed.

## FDA Emergency Use Authorization for Paxlovid

On December 22, 2021, FDA announced Emergency Use Authorization (EUA) for Paxlovid[1,2] for the oral treatment of mild to moderate COVID-19. Paxlovid is a combination of nirmatrelvir (a SARS-CoV-2 protease inhibitor) and ritonavir (an HIV-1 protease inhibitor and CYP3A4 and P-glycoprotein inhibitor). Paxlovid is indicated for adults and children (≥12 years and weighing ≥40 kg). Dosing is three tablets (two 150 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir) twice daily, for a maximum of 5 days.

## Considerations for Patients on Antiseizure Medications

There are two major considerations when Paxlovid is given to patients taking some antiseizure medications (ASMs), consistent with previously documented interactions of

**Table 1.** Antiseizure Medications Enzymatic Considerations.

| Enzyme | Substrates | Enzyme Inhibitors | Enzyme Inducers |
|---|---|---|---|
| CYP3A4 | cannabidiol, carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, everolimus, felbamate, lacosamide, midazolam, oxcarbazepine, perampanel, stiripentol, tiagabine, zonisamide | | carbamazepine, eslicarbazepine, felbamate, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, stiripentol, topiramate |
| CYP2C19 | brivaracetam, cannabidiol, clobazam, diazepam, lacosamide, phenobarbital, phenytoin, primidone, stiripentol, valproate, zonisamide | cannabidiol, eslicarbazepine, felbamate, topiramate, valproate | carbamazepine, phenobarbital, phenytoin, primidone, stiripentol |
| CYP2C9 | carbamazepine, lacosamide, phenobarbital, primidone, valproate | perampanel, stiripentol, valproate | carbamazepine, phenobarbital, primidone |
| CYP2B6 | clobazam, perampanel, valproate | | carbamazepine, perampanel |
| CYP1A2 | stiripentol | cannabidiol, stiripentol | |
| UGT | cannabidiol, diazepam, lamotrigine, oxcarbazepine | valproate | lamotrigine, phenobarbital, primidone |

ASMs and antiretroviral drugs, including ritonavir.[3] The first major consideration is the effect of some ASMs on Paxlovid. The ASMs **carbamazepine**, **phenobarbital**, **phenytoin**, and **primidone** (although primidone is not listed in the EUA) are **contraindicated**, because they are strong inducers of the CYP3A4 isozymes that metabolize Paxlovid.[4] Due to the strong enzymatic induction caused by these medications, there is concern for possible loss of virologic response to Paxlovid and development of resistance.

Paxlovid needs to be started soon after diagnosis of COVID-19. Clinically, if patients were to stop taking these strong enzyme-inducing ASMs, the time-dependent process of de-induction of CYP3A4 isozymes would take more time than is likely feasible, so other treatments for COVID-19, including molnupiravir or IV therapies like remdesivir,[5] may be appropriate. The EUA for molnupiravir,[6] another COVID-19 oral therapy for patients ≥18 years old, states that the drug is not a substrate of CYP enzymes or major drug transporters, and in vitro studies do not suggest inhibitory actions.

Paxlovid should be used with caution with ASMs that are weak to moderate inducers of CYP3A4. ASMs in this category that *may* affect Paxlovid effectiveness include the following: **cenobamate**, **eslicarbazepine**, **oxcarbazepine**, **rufinamide**, and **topiramate**. See Table 1 for a full list of ASMs that are CYP3A4 inducers.

The second major consideration is the effect of Paxlovid on the plasma levels of several drugs**.** ASMs that are primarily metabolized by CYP3A4 are listed in the top left cell of Table 1. Patients receiving these ASMs may warrant closer monitoring while being treated with Paxlovid**.** Because ritonavir is a potent, mechanism-based inhibitor (irreversible) of CYP3A4, Paxlovid may increase plasma concentrations of these drugs. Co-administration of Paxlovid with drugs that are extensively metabolized by CYP3A4 and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Of note, because of its mechanism, ritonavir de-inhibition will be slower in offset, and inhibition of metabolism by CYP3A4 may persist for at least several days following Paxlovid discontinuation. Although perampanel is a major substrate for CYP3A4, short-term addition of CYP3A4 inhibitors is unlikely to have lasting impact on perampanel concentrations due to its very long half-life.

Paxlovid (specifically ritonavir) can also inhibit P-Glycoprotein (PGP), a drug transport protein, which may impact bioavailability of some ASMs.[7,8] Patients receiving these medications may warrant closer monitoring while being treated with Paxlovid. In particular, use of Paxlovid with everolimus (which is a substrate of both 3A4 and PGP) may increase the risk of toxic adverse effects and may require a reduction in the dose of everolimus.

Ritonavir is a weak inducer of CYP1A2, CYP2C19, and CYP2C9, a moderate inducer of CYP2B6, and an inducer of UGT1A4. Notably, ritonavir combinations can significantly reduce lamotrigine plasma concentrations, presumably via induction of glucuronidation; however, data for Paxlovid are not yet available, and the clinical relevance during the short duration of Paxlovid treatment is unclear. Monitoring of lamotrigine plasma concentrations may be warranted in patients receiving Paxlovid therapy. Formulations that contain ritonavir may reduce plasma concentrations of other ASMs that are substrates of these isoenzymes, as specified in Table 1.

Additional important information for AES members about Paxlovid and ASMs is highlighted in Table 1, with the caveat that specific pharmacokinetic/pharmacodynamic (PK/PD) data and clinical outcome data are not yet available on Paxlovid for people with epilepsy.

A more complete summary of other ASM pharmacokinetics and drug interactions may be found in the AES 2020 update of *A Summary of Antiseizure Medications Available in the United States*.[9]

## Guidance to American Epilepsy Society Members and American Epilepsy Society Monitoring

Given the known interactions, AES members should closely monitor patients taking any of these several ASMs while taking Paxlovid for signs and symptoms of toxicity and make appropriate dose adjustments.

In addition to the fact sheet on the Paxlovid EUA,[2] available FDA resources include a provider letter[10] and FAQ,[11] information for patients with moderate renal impairment,[10,12] and the EUA scientific review information,[13,14] as well as a fact sheet for patients, parents, and caregivers, available in English and Spanish.[15]

The AES Treatments Committee will continue to monitor the latest information on known interactions for Paxlovid and other newer antiretroviral drugs and will alert AES members as new information or further guidance becomes available. Updates to other AES COVID-19–related documents are underway and will be disseminated to members after review by the committee and Council.

### Declaration of Conflicting Interests

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### References

1. U.S. Food & Drug Administration. *Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19*. Press Release. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19. Published December 22, 2021. Accessed January 18, 2022.
2. U.S. Food & Drug Administration. *Fact sheet for health care providers: Emergency Use Authorization for Paxlovid™*. https://www.fda.gov/media/155050/download. Published December 22, 2021. Accessed January 18, 2022.
3. Birbeck GL, French JA, Perucca E, et al. Evidence-based guideline: Antiepileptic drug selection for people with HIV/AIDS: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. *Neurology* 2012;78(2):139-145. doi:10.1212/WNL.0b013e31823efcf8.
4. University of Liverpool. University of Liverpool COVID-19 Drug Interactions tool. Pharmacology Research Labs, Liverpool Drug Interactions Group. Interactions report. [Report run for interactions between Paxlovid and a selected list of 17 antiseizure medication formulations, January 1, 2022]. https://www.covid19-druginteractions.org/. Accessed January 18, 2022.
5. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med* 2022; 386(4):305-315. doi:10.1056/NEJMoa2116846.
6. U.S. Food & Drug Administration. *Fact Sheet for Health Care Providers: Emergency Use Authorization for Lagevrio™* (molnupiravir). December 22, 2021. *Revised* March, 2022. Accessed March 24, 2022.
7. Luna-Tortós C, Fedrowitz M, Löscher W. Several major antiepileptic drugs are substrates for human P-glycoprotein. *Neuropharmacology*. 2008;55(8):1364-1375. doi:10.1016/j.neuropharm.2008.08.032.
8. French JA. P-glycoprotein expression and antiepileptic drug resistance. *Lancet Neurol*. 2013;12(8):732-733. doi:10.1016/S1474-4422(13)70128-5.
9. American Epilepsy Society. Vossler DG, Gidal BE, AES Treatments Committee. A summary of antiseizure medications available in the United States. 2020 update. https://www.aesnet.org/docs/default-source/pdfs-clinical/2020-september-aes_summary_of_asms.pdf?sfvrsn=c1a0ed0b_2. Published September 10, 2020. Accessed January 28, 2022.
10. U.S. Food & Drug Administration. *Dear healthcare provider letter. Important prescribing information. Subject: PAXLOVID Emergency Use Authorization (EUA) dosing and dispensing in moderate renal impairment, and risk of serious adverse reactions due to drug interactions*. https://www.fda.gov/media/155071/download. Published December 22, 2021. Accessed January 18, 2022.
11. U.S. Food & Drug Administration. *Frequently asked questions on the Emergency Use Authorization for PaxlovidTM for treatment of COVID-19*. https://www.fda.gov/media/155052/download. Published December 22, 2021. Accessed January 18, 2022.
12. Pfizer. North America Medical Affairs. *Important PaxlovidTM EUA dispensing information for patients with moderate renal impairment*. https://www.fda.gov/media/155071/download. Published December 22, 2021. Accessed January 18, 2022.
13. U.S. Food & Drug Administration (from Pfizer Labs). *Emergency Use Authorization (EUA) review for Paxlovid (nirmatrelvir tablets*

*copackaged with ritonavir tablets). Center for Drug Evaluation and Research (CDER) Review.* https://www.fda.gov/media/155194/download. Published December 22, 2021. Accessed January 18, 2022.

14. U.S. Food & Drug Administration. *CDER scientific review documents supporting Emergency Use Authorizations for drug and biological therapeutic products | COVID-19* [FDA portal]. https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological. Accessed January 18, 2022.
15. U.S. Food & Drug Administration. *FDA fact sheet for patients, parents, and caregivers. Emergency Use Authorization (EUA) on Paxlovid for coronavirus disease 2019 (COVID-19)*. https://www.fda.gov/media/155051/download. Published December 22, 2021. Accessed January 18, 2022.