Paxlovid and Lagevrio Overview for Healthcare Professionals

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What are Paxlovid and Lagevrio?

- Paxlovid (Nirmatrelvir/Ritonavir) and Lagevrio (Molnupiravir) are oral antiviral medications currently used to treat mild to moderate COVID-19

- The FDA issued an emergency use authorization for Paxlovid (December 22, 2021) and Lagevrio (December 23, 2021), but they are not currently FDA approved for the treatment of COVID-19

- Paxlovid is manufactured by Pfizer and Lagevrio is manufactured by Merck

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVIDTM. (n.d.). Retrieved May 24, 2022, from https://www.fda.gov/media/155050/download?ACSTrackingID=USCDC_511-DM72818&ACSTrackingLabel=HAN%20461-%20COCA%20Subscribers&deliveryName=USCDC_511-DM72818
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What is an Emergency Use Authorization?

About Emergency Use Authorizations (EUAs)

The Emergency Use Authorization (EUA) authority allows FDA to help strengthen the nation's public health protections against chemical, biological, radiological, and nuclear (CBRN) threats including infectious diseases, by facilitating the availability and use of medical countermeasures (MCMs) needed during public health emergencies.

Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when the Secretary of HHS declares that an emergency use authorization is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when certain criteria are met, including there are no adequate, approved, and available alternatives.

Commissioner, O. of the. (n.d.). Emergency use authorization. U.S. Food and Drug Administration. Retrieved June 2, 2022, from https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

IDSA Outpatient Treatment Guidelines

COVID-19 OUTPATIENT TREATMENT GUIDELINES ROADMAP

COVID-19 Real-Time Learning Network

Brought to you by CDC and IDSA

Last Updated: May 3, 2022

This resource is intended to serve as a guide on available outpatient COVID-19 treatment options, with links to FDA Emergency Use Authorization information and guideline recommendations from national guideline-developing organizations, where available. **It is not intended to endorse or otherwise promote a specific clinical recommendation or course of action.** Additionally, it does not include other forms of guidance that may be available for specific subsets of populations. Finally, the guidelines referenced here may not consider local allocation and availability of scarce resources. Additional information on where to access these therapeutics can be found at the National Infusion Center Association[16] and HHS.[12]

Risk factors for severe COVID-19[11]

Included here are some medical conditions that may place patients at a higher risk for progression to severe COVID-19:

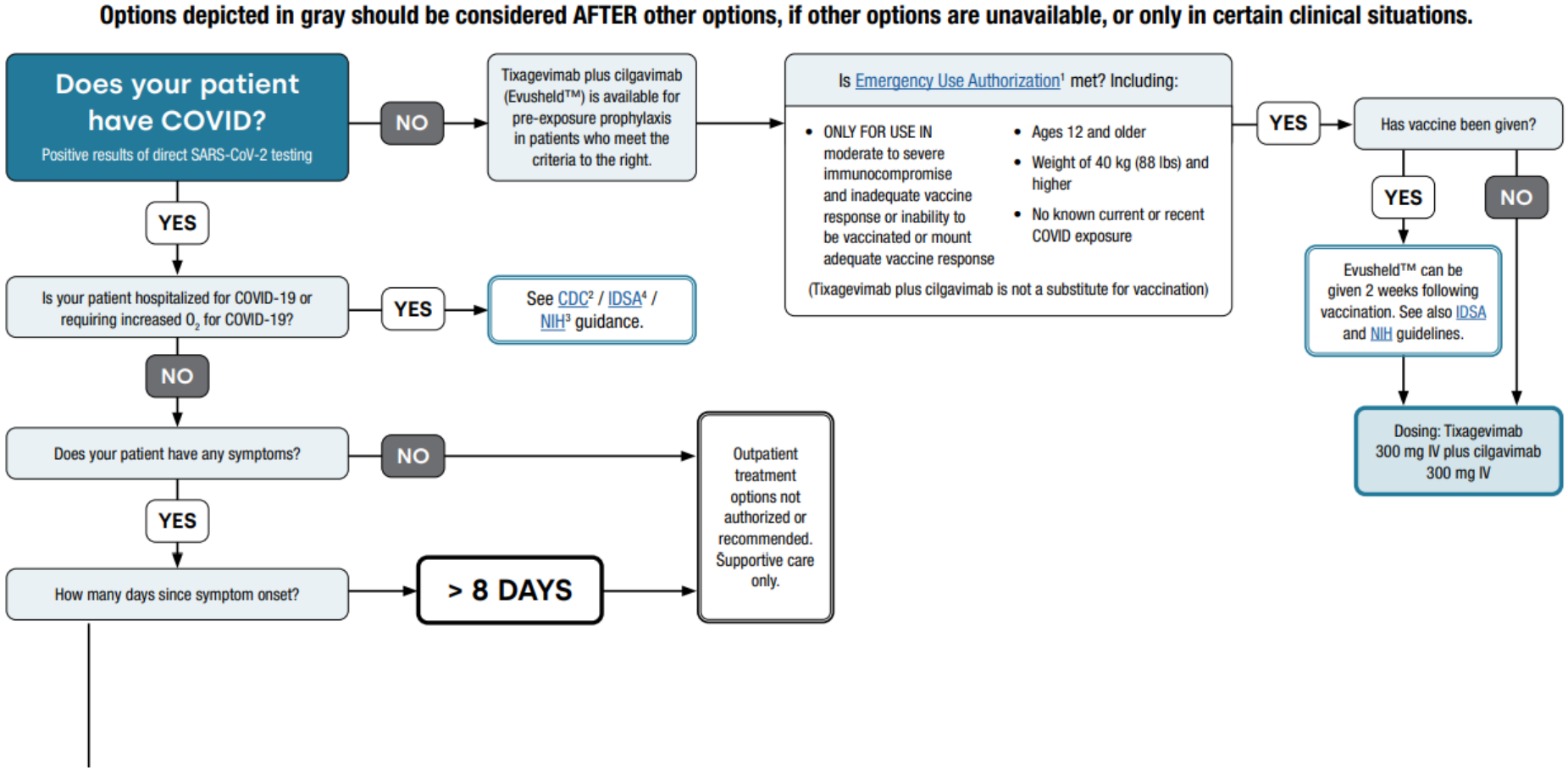
- Age 65 years and older
- BMI of more than 25 kg/m^2
- Pregnancy
- Chronic kidney disease
- Diabetes mellitus
- Immunosuppressing medications
- Cardiovascular disease or hypertension
- Chronic lung disease
- Sickle cell disease
- Neurodevelopmental disorders or conditions that confer medical complexity
- Medical technological dependence, e.g., tracheostomy

When giving products under Emergency Use Authorization, providers must:

1. Give patient fact sheet for patients.
2. Inform patient of alternatives to treatment.
3. Inform patient that this is an unapproved drug.

Covid-19 outpatient treatment roadmap - idsociety.org. (n.d.). Retrieved June 2, 2022, from https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/outpatientroadmap-v10.pdf

IDSA Outpatient Treatment Guidelines



Covid-19 outpatient treatment roadmap - idsociety.org. (n.d.). Retrieved June 2, 2022, from https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/outpatientroadmap-v10.pdf

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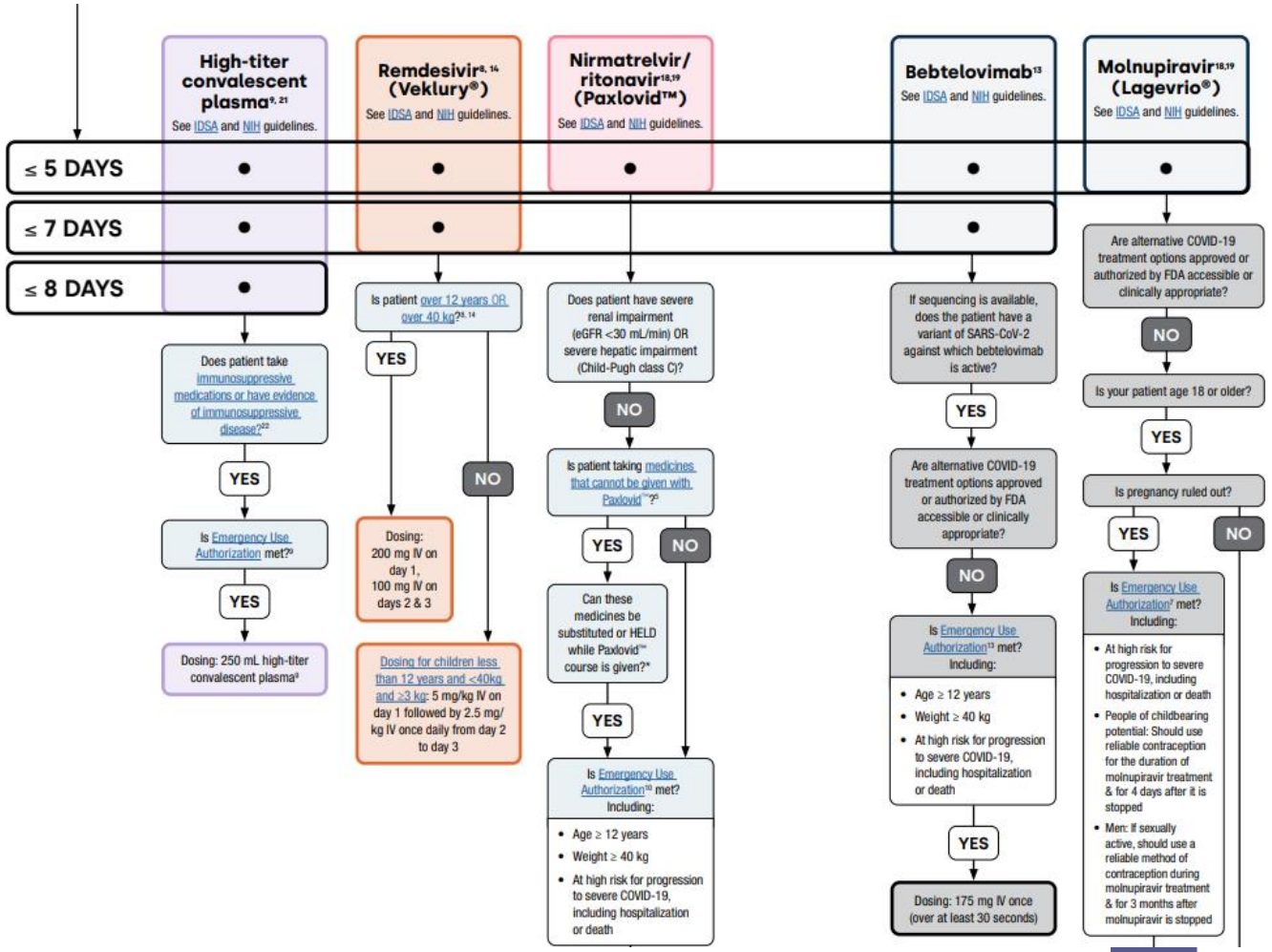

Covid-19 outpatient treatment roadmap - idsociety.org. (n.d.). Retrieved June 2, 2022, from https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/outpatientroadmap-v10.pdf

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Drug Comparison

Mechanism of Action

Paxlovid

- Nirmatrelvir is a SARS-CoV-2 main protease inhibitor and Ritonavir is a HIV-1 protease inhibitor and CYP3A inhibitor
- Ritonavir increases Nirmatrelvir's concentration in order to reach the target therapeutic range needed to sufficiently reduce viral replication

Lagevrio

- Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis
- Molnupiravir increases the frequency of viral RNA mutations, reducing viral replication

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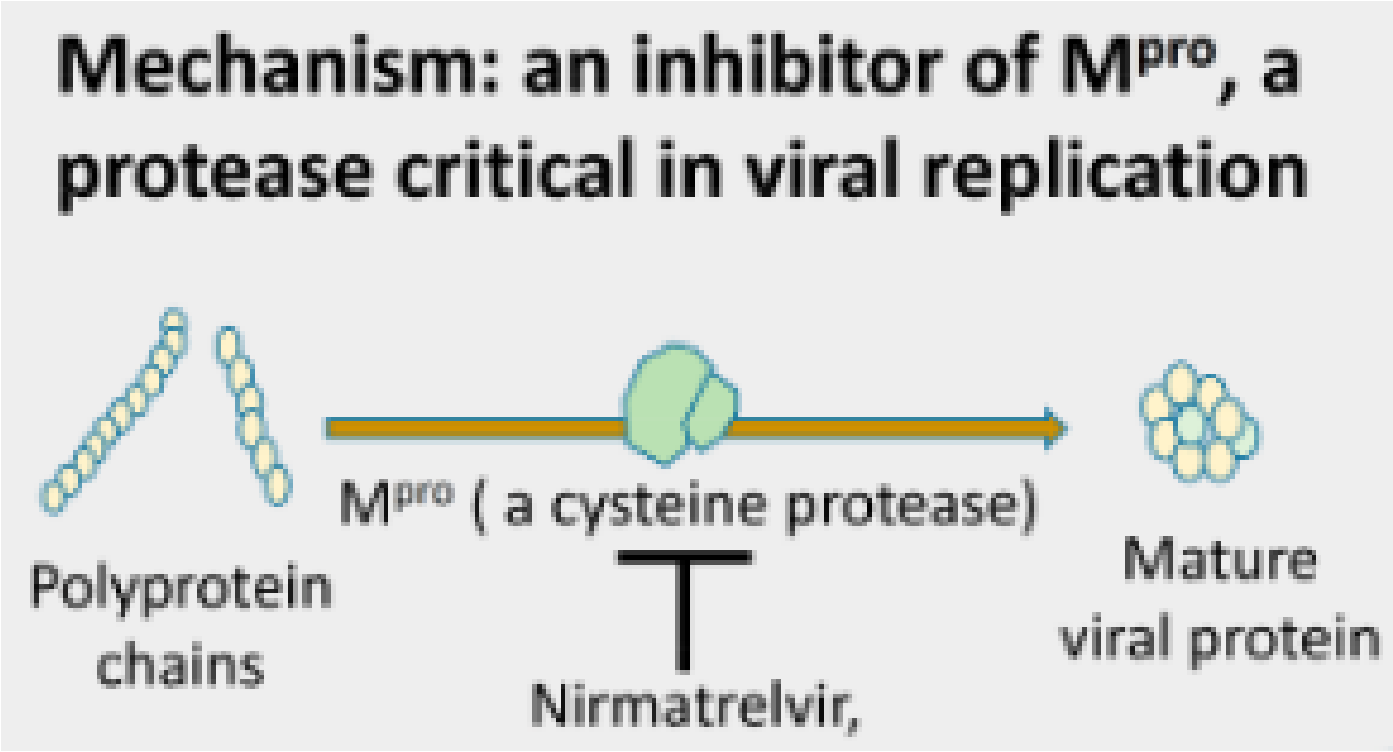
Mechanism of Action

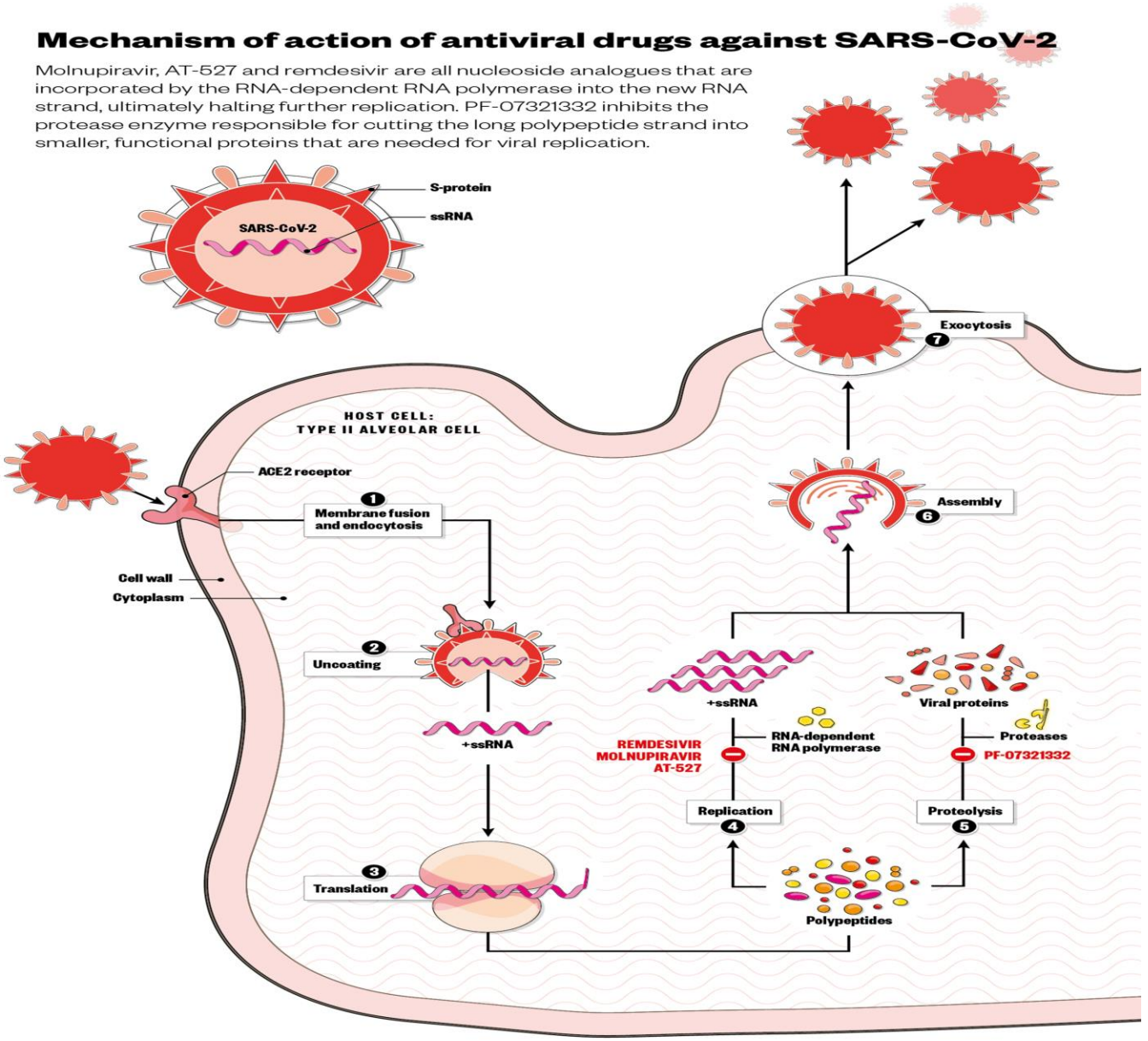
Paxlovid



Hung, Y.-P., Lee, J.-C., Chiu, C.-W., Lee, C.-C., Tsai, P.-J., Hsu, I.-L., & Ko, W.-C. (2022). Oral nirmatrelvir/ritonavir therapy for covid-19: The dawn in the dark? Antibiotics, 11(2), 220. https://doi.org/10.3390/antibiotics11020220

Mechanism of Action

Lagevrio



21 October 2021 By Christine Parry. (2022, February 9). *Antivirals for COVID-19: Five questions that must be answered*. The Pharmaceutical Journal. Retrieved June 2, 2022, from https://pharmaceutical-journal.com/article/feature/antivirals-for-covid-19-five-questions-that-must-be-answered

CYP3A

CYP3A

CYP3A is the most abundant, clinically significant group of cytochrome P-450 isoenzymes. The CYP3A group is composed of four major isoenzymes: CYP3A3, CYP3A4, CYP3A5, and CYP3A7. CYP3A4 is the most common and is implicated in the majority of drug interactions. However, since these enzymes are so closely related (having as much as 97% sequence homology), they often are referred to collectively by the subfamily name, CYP3A. Up to 60% of the liver's total cytochrome P-450 is CYP3A, and nearly 50% of all clinically relevant medications are metabolized by CYP3A. The presence of CYP3A in the small intestine results in decreased bioavailability of many ingested drugs. CYP3A inducers include the glucocorticoids, rifampin, carbamazepine, phenobarbital, and phenytoin. Among the many significant CYP3A inhibitors are grapefruit juice, erythromycin, ketoconazole, clarithromycin, and verapamil.

- CYP3A inducers can interact with Paxlovid by decreasing Nirmatrelvir concentrations to below target therapeutic ranges
- Since Ritonavir is a CYP3A inhibitor, it can increase concentrations of concomitant medications metabolized by CYP3A

Corkeron, M. (2008). Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose. *Anaesthesia and Intensive Care*, *36*(1), 130+. https://link.gale.com/apps/doc/A188796743/AONE?u=nysl_oweb&sid=googleScholar&xid=4f6e734d

Clearance

Paxlovid

Table 2: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (When Given With Ritonavir)	Ritonavir
Absorption		
T_{max} (h), median	3.00[a]	3.98[a]
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[c]
V_z/F (L), mean	104.7[b]	112.4[b]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F), mean	8.99[b]	13.92[b]
Metabolism		
Metabolic pathways	Minimal[d]	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	35.3%[e]	86.4%[f]
% drug-related material in urine	49.6%[e]	11.3%[f]

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Clearance

Paxlovid

Renal Impairment

No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of PAXLOVID is 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days *[see How Supplied/Storage and Handling (16)]. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID*. Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVIDTM. (n.d.). Retrieved May 24, 2022, from https://www.fda.gov/media/155050/download?ACSTrackingID=USCDC_511-DM72818&ACSTrackingLabel=HAN%20461-%20COCA%20Subscribers&deliveryName=USCDC_511-DM72818

Clearance

Lagevrio

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg LAGEVRIO Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)*	8260 (41.0)
C_{max} (ng/mL)*	2330 (36.9)
C_{12hr} (ng/mL)*	31.1 (124)
Pharmacokinetics in Healthy Subjects	
$AUC_{0\text{-}12hr}$ (ng*hr/mL)	8330 (17.9)
C_{max} (ng/mL)	2970 (16.8)
C_{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T_{max} (hr)†	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding (*in vitro*)	0%
Apparent Volume of Distribution (L)*	142
Elimination	
Effective $t_{1/2}$ (hr)	3.3
Apparent Clearance (L/hr)*	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)

Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated.
*Values were obtained from population PK analysis.
†Median [min - max]

- Molnupiravir is a 5´-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption
- NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP
- NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism.

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Clearance

Lagevrio

Renal Impairment

No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure *[see Clinical Pharmacology (12.3)]*.

Hepatic Impairment

No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure *[see Clinical Pharmacology (12.3)]*.

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Dosing

Paxlovid

- 300mg Nirmatrelvir (two 150mg tablets) with 100mg ritonavir (one 100mg tablet) taken together orally twice daily for 5 days
- Patients with moderate renal impairment (GFR= 30-60mL/min) should take 150mg Nirmatrelvir and 100mg ritonavir together orally twice daily for 5 days
- Initiate as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset
- Not authorized for use for longer than 5 consecutive days

Lagevrio

- 800mg (four 200mg capsules) taken orally every 12 hours for 5 days
- Initiate as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset
- Not authorized for use for longer than 5 consecutive days

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Eligibility

Paxlovid

- Mild to moderate COVID-19
- Positive COVID-19 test (Antigen or PCR)

  *Can be rapid at-home test
- High risk for progression to severe COVID-19
- 12 years and older weighing at least 40kg

Lagevrio

- Mild to moderate COVID-19
- Positive COVID-19 test (Antigen or PCR)

  *Can be rapid at-home test
- High risk for progression to severe COVID-19
- 18 years or older

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Pricing

Paxlovid

- Currently free of charge to eligible patients with or without insurance
- One course costs the federal government $530 on average
- Prescription only

Lagevrio

- Currently free of charge to eligible patients with or without insurance
- One course costs the federal government $700 on average
- Prescription only

Hoffman, J. (2021, November 11). Covid News: U.S. parents' views are shifting on vaccines. The New York Times. Retrieved June 2, 2022, from https://www.nytimes.com/live/2021/09/30/world/covid-delta-variant-vaccines#merck-antiviral-pill-covid
Robbins, R. (2022, January 19). When my mom got covid, I went searching for pfizer's Pills. The New York Times. Retrieved June 2, 2022, from https://www.nytimes.com/2022/01/19/business/covid-pill-treatment-pfizer.html

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Side effects

Paxlovid

- Dysgeusia (Altered sense of taste)
- Diarrhea
- Hypertension
- Myalgia (Muscle aches)

Lagevrio

- Diarrhea
- Nausea
- Dizziness
- Rash

Hammond, J., Leister-Tebbe, H., Gardner, A., Abreu, P., Bao, W., Wisemandle, W., Baniecki, M. L., Hendrick, V. M., Damle, B., Simón-Campos, A., Pypstra, R., & Rusnak, J. M. (2022). Oral Nirmatrelvir for high-risk, nonhospitalized adults with covid-19. New England Journal of Medicine, 386(15), 1397–1408. https://doi.org/10.1056/nejmoa2118542
Bernal, Angélica Jayk, et al. "Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients." New England Journal of Medicine, vol. 386, no. 6, 10 Feb. 2022, https://doi.org/10.1056/NEJMoa2116044.

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Paxlovid COVID Rebound

CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
May 24, 2022, 9:00 AM ET
CDCHAN-0467

COVID-19 Rebound After Paxlovid Treatment

Summary
The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to update healthcare providers, public health departments, and the public on the potential for recurrence of COVID-19 or "COVID-19 rebound." **Paxlovid continues to be recommended for early-stage treatment of mild to moderate COVID-19 among persons at high risk for progression to severe disease**. Paxlovid treatment helps prevent hospitalization and death due to COVID-19. COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. **A brief return of symptoms may be part of the natural history of SARS-CoV-2 (the virus that causes COVID-19) infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status**. Limited information currently available from case reports suggests that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness; there are no reports of severe disease. There is currently no evidence that additional treatment is needed with Paxlovid or other anti-SARS-CoV-2 therapies in cases where COVID-19 rebound is suspected.

Regardless of whether the patient has been treated with an antiviral agent, risk of transmission during COVID-19 rebound can be managed by following CDC's guidance on isolation, including taking other precautions such as masking.

Staying up to date with COVID-19 vaccination lowers the risk of getting COVID-19 and helps prevent serious outcomes of COVID-19, such as severe illness, hospitalization, and death.

Centers for Disease Control and Prevention. (2019, March 28). *2022 Hans*. Centers for Disease Control and Prevention. Retrieved June 2, 2022, from https://emergency.cdc.gov/han/2022.asp

Paxlovid COVID Rebound

Recommendations for Healthcare Providers

For patients with COVID-19 rebound

- There is currently no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound. Based on data available at this time, patient monitoring continues to be the most appropriate management for patients with recurrence of symptoms after completion of a treatment course of Paxlovid.
- Advise people with COVID-19 rebound to follow CDC's guidance on isolation and take precautions to prevent further transmission. Patients should re-isolate for at least 5 days. Per CDC guidance, they can end their re-isolation period after 5 full days if fever has resolved for 24 hours (without the use of fever-reducing medication) and symptoms are improving. The patient should wear a mask for a total of 10 days after rebound symptoms started.
- Consider clinical evaluation of patients who have COVID-19 rebound and symptoms that persist or worsen.
- Healthcare providers are encouraged to report cases of COVID-19 rebound to Pfizer after Paxlovid treatment using the following online tool: Pfizer Safety Reporting and to FDA MedWatch. Complete and submit a MedWatch form, or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178). Call 1-800-FDA-1088 for questions.

For patients just diagnosed with COVID-19

- Healthcare providers should counsel patients on available COVID-19 treatment options, particularly for those patients at increased risk of developing severe COVID-19.
- Paxlovid should be considered for any patient who meets the eligibility criteria. For information on Paxlovid eligibility, refer to FDA's Fact Sheet for Healthcare Providers.
- Due to the potential for severe drug-drug interactions with the ritonavir component of Paxlovid, it is strongly suggested that healthcare providers not experienced in prescribing this drug refer to the Fact Sheet for Healthcare Providers, the Paxlovid Patient Eligibility Screening Checklist Tool for Prescribers, and the NIH Statement on Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines. Healthcare providers can also contact a local clinical pharmacist or infectious disease specialist for advice.

Centers for Disease Control and Prevention. (2019, March 28). *2022 Hans*. Centers for Disease Control and Prevention. Retrieved June 2, 2022, from https://emergency.cdc.gov/han/2022.asp

Contraindications

Paxlovid

- History of clinically significant hypersensitivity reactions to Nirmatrelvir or Ritonavir
- Co-administration of drugs highly dependent on CYP3A for clearance or potent CYP3A inducers

Lagevrio

- No contraindications have been identified based on the limited available data

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Monitoring

- When taking these medications patients should be monitored for hypersensitivity reactions including angioedema, anaphylaxis, and severe skin reactions
- Patients on Paxlovid should be monitored for liver function and HIV status should be determined prior to prescribing
- Molnupiravir patients should be monitored for pregnancy and should be advised to use a reliable method of contraception for the duration of treatment and for 4 days after the last dose of Lagevrio

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Drug interactions for Paxlovid (Prescribe Alternate Therapy)

- Anticonvulsants
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Primidone
- Anti-infective Agents
  - Glecaprevir/pibrentasvir
  - Rifampin
  - Rifapentine
- Immunosuppressants
  - Voclosporin
- Neuropsychiatric agents
  - Clozapine
  - Lumateperone
  - Lurasidone
  - Midazolam (oral)
  - Pimozide

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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Drug interactions for Paxlovid

- Cardiovascular Agents
  - Amiodarone
  - Clopidogrel
  - Disopyramide
  - Dofetilide
  - Dronedarone
  - Eplerenone
  - Flecainide
  - Ivabradine
  - Propafenone
  - Quinidine
- Pain Medications
  - Meperidine (pethidine)
- Pulmonary Hypertension Medications
  - Sildenafil
  - Tadalafil
  - Vardenafil

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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Drug interactions for Paxlovid

- Miscellaneous
  - Bosentan
  - Certain chemotherapeutic agents
  - Ergot derivatives
  - Lumacaftor/ivacaftor
  - St. John’s wort
  - Tolvaptan

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Other Drugs with Established and Other Potentially Significant Drug Interactions with PAXLOVID (listed alphabetically by generic name)

Interaction Codes:

XXX — Coadministration of this drug with PAXLOVID is CONTRAINDICATED. XXX For further information, refer to the Fact Sheet for Healthcare Providers and the individual Prescribing Information for the drug.

*** — Coadministration of this drug with PAXLOVID should be avoided *** and/or holding of this drug, dose adjustment of this drug, or special monitoring is necessary. Consultation with the prescriber of the potentially interacting drug is recommended. For further information, refer to the Health Care Provider Fact Sheet and the individual Prescribing Information for the drug.

Drug	Drug Class	Interaction Code
abemaciclib	Anticancer drug	***
alfuzosin	Alpha 1-adrenoreceptor antagonist	XXX
amiodarone	Antiarrhythmic	XXX
amlodipine	Calcium channel blocker	***
apalutamide	Anticancer drug	XXX
bedaquiline	Antimycobacterial	***
bepridil	Antiarrhythmic	***
betamethasone	Systemic corticosteroid	***
bosentan	Endothelin receptor antagonist	***
budesonide	Systemic corticosteroid	***
bupropion	Antidepressant	***
carbamazepine	Anticonvulsant	XXX
ceritinib	Anticancer drug	***
ciclesonide	Systemic corticosteroid	***
clarithromycin	Anti-infective	***
clozapine	Antipsychotic	XXX
colchicine	Anti-gout	XXX

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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cyclosporine	Immunosuppressant	***
dabigatran	Anticoagulants	***
dasabuvir	Hepatitis C direct acting antiviral	***
dasatinib	Anticancer drug	***
dexamethasone	Systemic corticosteroid	***
digoxin	Cardiac glycoside	***
dihydroergotamine	Ergot derivative	XXX
diltiazem	Calcium channel blocker	***
dronedarone	Antiarrhythmic	XXX
elbasvir/grazoprevir	Hepatitis C direct acting antiviral	***
encorafenib	Anticancer drug	***
ergotamine	Ergot derivative	XXX
erythromycin	Anti-infective	***
felodipine	Calcium channel blocker	***

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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Drug	Drug Class	Interaction Code
fentanyl	Narcotic analgesic	***
flecainide	Antiarrhythmic	XXX
fluticasone	Systemic corticosteroid	***
glecaprevir/pibrentasvir	Hepatitis C direct acting antiviral	***
ibrutinib	Anticancer drug	***
isavuconazonium sulfate	Antifungal	***
itraconazole	Antifungal	***
ivosidenib	Anticancer drug	***
ketoconazole	Antifungal	***
lidocaine (systemic)	Antiarrhythmic	***
lurasidone	Antipsychotic	XXX
methadone	Narcotic analgesic	***
methylergonovine	Ergot derivative	XXX
methylprednisolone	Systemic corticosteroid	***
midazolam (administered parentally)	Sedative/hypnotic	***
midazolam (oral)	Sedative/hypnotic	XXX
mometasone	Systemic corticosteroid	***
neratinib	Anticancer drug	***
nicardipine	Calcium channel blocker	***

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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nifedipine	Calcium channel blocker	***
nilotinib	Anticancer drug	***
ombitasvir/paritaprevir /ritonavir	Hepatitis C direct acting antiviral	***
pethidine	Analgesic	XXX
phenobarbital	Anticonvulsant	XXX
phenytoin	Anticonvulsant	XXX
pimozide	Antipsychotic	XXX
prednisone	Systemic corticosteroid	***
propafenone	Antiarrhythmic	XXX
propoxyphene	Analgesic	XXX
quetiapine	Antipsychotic	***
quinidine	Antiarrhythmic	XXX
ranolazine	Antianginal	XXX
rifabutin	Antimycobacterial	***
rifampin	Antimycobacterial	XXX
rivaroxaban	Anticoagulant	***
salmeterol	ong-acting beta-adrenoceptor agonist	***
sildenafil (Revatio®) when used for pulmonary arterial hypertension	PDE5 inhibitor	XXX

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

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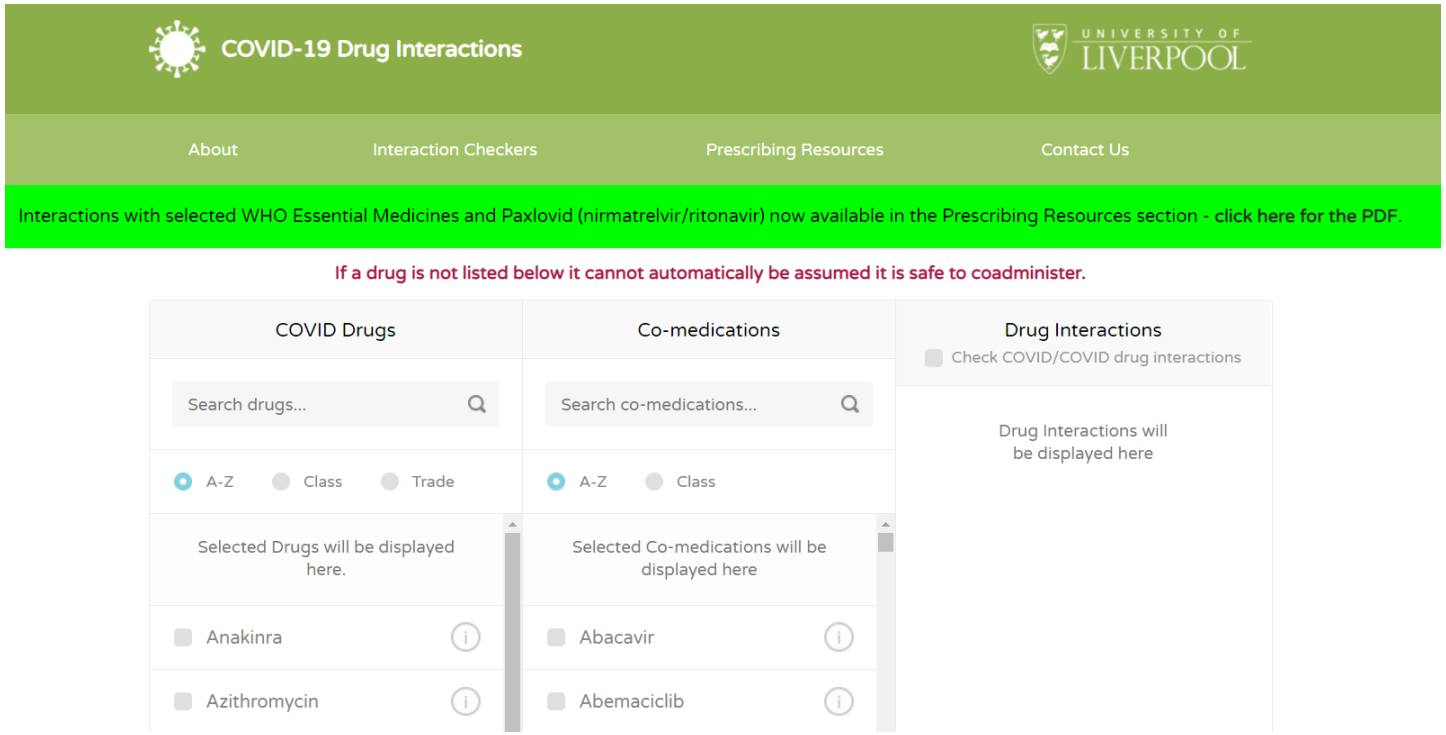
sirolimus	Immunosuppressant	***
sofosbuvir/velpatasvir/ voxilaprevir	Hepatitis C direct acting antiviral	***
St. John's Wort (hypericum perforatum)	Herbal product	XXX
tacrolimus	Immunosuppressant	***
trazodone	Antidepressant	***
triamcinolone	Systemic corticosteroid	***
triazolam	Sedative/hypnotic	XXX
venetoclax	Anticancer drug	***
vinblastine	Anticancer drug	***
vincristine	Anticancer drug	***
voriconazole	Antifungal	***
warfarin	Anticoagulant	***

U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

COVID-19 Drug Interaction Checker

- University of Liverpool offers an online COVID-19 Drug Interaction Checker that can be utilized to check for drug interactions



Liverpool covid-19 interactions. Liverpool COVID-19 Interactions. (n.d.). Retrieved June 2, 2022, from https://www.covid19-druginteractions.org/checker

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Drug interactions for Lagevrio

- No drug interactions have been identified based on the limited available data

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES. (n.d.). Retrieved May 24, 2022, from https://www.fda.gov/media/155054/download

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Paxlovid Study

- International phase 2-3 double blind, randomized, controlled trial
- Unvaccinated patients with mild to moderate COVID-19 who were at high risk for progression to severe COVID-19
- 2246 adults randomly assigned Paxlovid or placebo every 12 hours for 5 days within 5 days of symptom onset

Results

- 88.9% relative risk reduction from Paxlovid in comparison to placebo when treated 3 days or less from the onset of symptoms
- Similar adverse event incidence in both Paxlovid and placebo groups, however dysgeusia and diarrhea were more frequent with Paxlovid

Hammond, J., Leister-Tebbe, H., Gardner, A., Abreu, P., Bao, W., Wisemandle, W., Baniecki, M. L., Hendrick, V. M., Damle, B., Simón-Campos, A., Pypstra, R., & Rusnak, J. M. (2022). Oral Nirmatrelvir for high-risk, nonhospitalized adults with covid-19. New England Journal of Medicine, 386(15), 1397–1408. https://doi.org/10.1056/nejmoa2118542

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Paxlovid Study

Treated ≤3 Days after Onset of Symptoms through Day 28 (modified intention-to-treat population)

	Nirmatrelvir Group N = 697	Placebo Group N = 682
Total number of patients with event	5	44
Covid-19–related hospitalization	5	44
Death from any cause	0	9
Estimated percentage with event (95% CI)	0.72 (0.30–1.73)	6.53 (4.90–8.68)
Difference ±SE from placebo — percentage points	–5.81±1.01	
Relative risk reduction	88.9%	

Adverse Events during Treatment Period (safety-analysis population)

	Nirmatrelvir Group N = 1109	Placebo Group N = 1115
No. of adverse events	476	525
Patients with any adverse event — no. (%)	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13 (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)

Hammond, J., Leister-Tebbe, H., Gardner, A., Abreu, P., Bao, W., Wisemandle, W., Baniecki, M. L., Hendrick, V. M., Damle, B., Simón-Campos, A., Pypstra, R., & Rusnak, J. M. (2022). Oral Nirmatrelvir for high-risk, nonhospitalized adults with covid-19. New England Journal of Medicine, 386(15), 1397–1408. https://doi.org/10.1056/nejmoa2118542

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Lagevrio Study

- Phase 3, double-blind, randomized, placebo-controlled trial
- Unvaccinated patients with mild to moderate COVID-19 with at least one risk factor for severe COVID-19 illness
- 1433 participants randomly assigned Molnupiravir or placebo twice daily for 5 days within 5 days of symptom onset

Results

- Molnupiravir group had 6.8% risk of hospitalization or death compared to 9.7% in the placebo group. The Molnupiravir group had a 3% absolute risk reduction and a 30% relative risk reduction.
- Similar adverse event incidence in both Molnupiravir and placebo groups, with diarrhea, nausea, and dizziness being the most frequently reported adverse events related to the trial regimen

Bernal, Angélica Jayk, et al. "Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients." New England Journal of Medicine, vol. 386, no. 6, 10 Feb. 2022, https://doi.org/10.1056/NEJMoa2116044.

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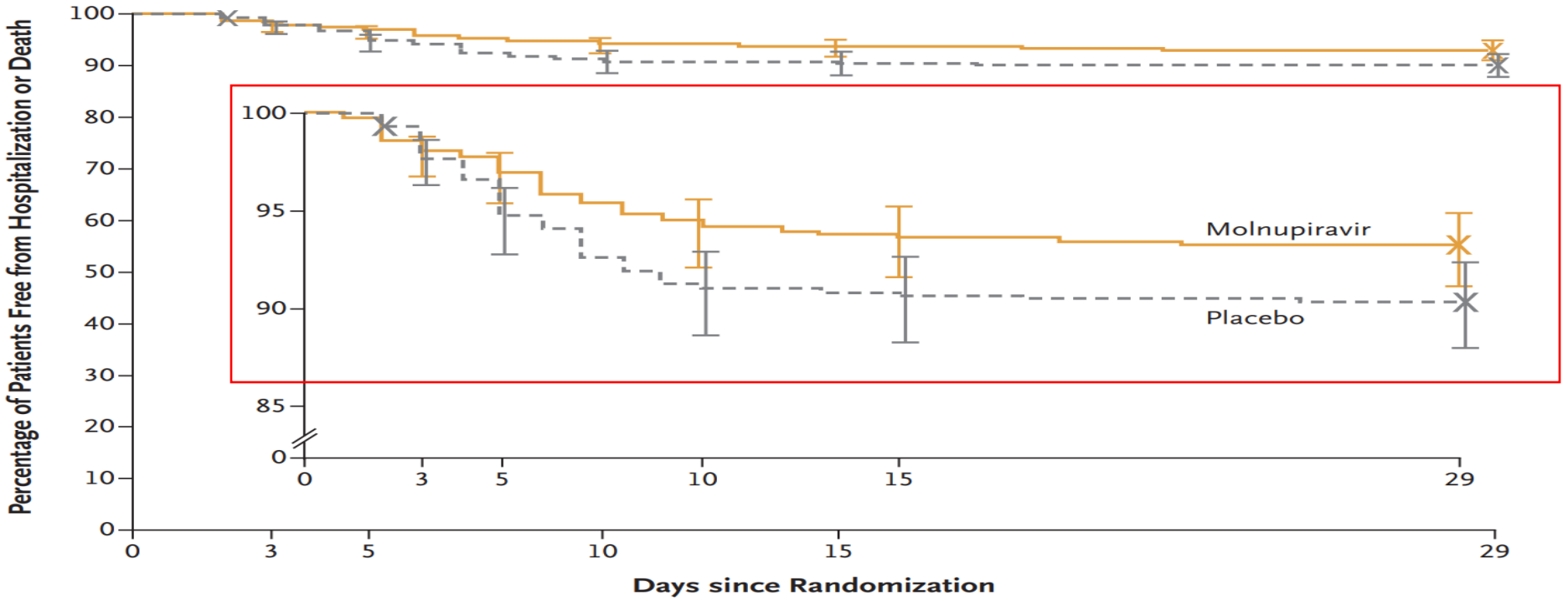
Lagevrio Study



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

Bernal, Angélica Jayk, et al. "Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients." New England Journal of Medicine, vol. 386, no. 6, 10 Feb. 2022, https://doi.org/10.1056/NEJMoa2116044.

Lagevrio Study

Table 2. Incidence of Adverse Events in the Safety Population.

Adverse Events and Discontinuation	Molnupiravir (N = 710)	Placebo (N = 701)	Estimated Difference (95% CI)*
	number (percent)		*percentage points*
Participants with adverse events			
≥1 Adverse event	216 (30.4)	231 (33.0)	−2.5 (−7.4 to 2.3)
≥1 Adverse event related to the assigned regimen†	57 (8.0)	59 (8.4)	−0.4 (−3.3 to 2.5)
≥1 Serious adverse event	49 (6.9)	67 (9.6)	−2.7 (−5.6 to 0.2)
≥1 Serious adverse event related to the assigned regimen†	0	1 (0.1)	−0.1 (−0.8 to 0.4)
Death	2 (0.3)	12 (1.7)	−1.4 (−2.7 to −0.5)
Participants who discontinued the assigned regimen because of an adverse event			
Adverse event	10 (1.4)	20 (2.9)	−1.4 (−3.1 to 0.1)
Adverse event related to the assigned regimen†	4 (0.6)	3 (0.4)	0.1 (−0.8 to 1.1)
Serious adverse event	5 (0.7)	13 (1.9)	−1.2 (−2.5 to 0.0)
Serious adverse event related to the assigned regimen†	0	0	0.0 (−0.5 to 0.5)

Bernal, Angélica Jayk, et al. "Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients." New England Journal of Medicine, vol. 386, no. 6, 10 Feb. 2022, https://doi.org/10.1056/NEJMoa2116044.

References

- Hoffman, J. (2021, November 11). Covid News: U.S. parents' views are shifting on vaccines. The New York Times. Retrieved June 2, 2022, from https://www.nytimes.com/live/2021/09/30/world/covid-delta-variant-vaccines#merck-antiviral-pill-covid
- Robbins, R. (2022, January 19). When my mom got covid, I went searching for pfizer's Pills. The New York Times. Retrieved June 2, 2022, from https://www.nytimes.com/2022/01/19/business/covid-pill-treatment-pfizer.html
- U.S. Department of Health and Human Services. (n.d.). Paxlovid Drug-Drug Interactions. National Institutes of Health. Retrieved June 2, 2022, from https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/
- Centers for Disease Control and Prevention. (2019, March 28). 2022 Hans. Centers for Disease Control and Prevention. Retrieved June 2, 2022, from https://emergency.cdc.gov/han/2022.asp
- Hung, Y.-P., Lee, J.-C., Chiu, C.-W., Lee, C.-C., Tsai, P.-J., Hsu, I.-L., & Ko, W.-C. (2022). Oral nirmatrelvir/ritonavir therapy for covid-19: The dawn in the dark? Antibiotics, 11(2), 220. https://doi.org/10.3390/antibiotics11020220
- 21 October 2021 By Christine Parry. (2022, February 9). *Antivirals for COVID-19: Five questions that must be answered*. The Pharmaceutical Journal. Retrieved June 2, 2022, from https://pharmaceutical-journal.com/article/feature/antivirals-for-covid-19-five-questions-that-must-be-answered

References

- FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVIDTM. (n.d.). Retrieved May 24, 2022, from https://www.fda.gov/media/155050/download?ACSTrackingID=USCDC_511-DM72818&ACSTrackingLabel=HAN%20461-%20COCA%20Subscribers&deliveryName=USCDC_511-DM72818
- FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES. (n.d.). Retrieved May 24, 2022, from https://www.fda.gov/media/155054/download
- Hammond, J., Leister-Tebbe, H., Gardner, A., Abreu, P., Bao, W., Wisemandle, W., Baniecki, M. L., Hendrick, V. M., Damle, B., Simón-Campos, A., Pypstra, R., & Rusnak, J. M. (2022). Oral Nirmatrelvir for high-risk, nonhospitalized adults with covid-19. New England Journal of Medicine, 386(15), 1397–1408. https://doi.org/10.1056/nejmoa2118542
- Bernal, Angélica Jayk, et al. “Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients.” New England Journal of Medicine, vol. 386, no. 6, 10 Feb. 2022, https://doi.org/10.1056/NEJMoa2116044.
- Covid-19 outpatient treatment roadmap - idsociety.org. (n.d.). Retrieved June 2, 2022, from https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/outpatientroadmap-v10.pdf
- Liverpool covid-19 interactions. Liverpool COVID-19 Interactions. (n.d.). Retrieved June 2, 2022, from https://www.covid19-druginteractions.org/checker