Notable Updates for COVID-19

RISE
Reaching Impact, Saturation, and Epidemic Control

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FACT SHEET: Oral Antivirals

Paxlovid (Nirmatrelvir with Ritonavir)

Category of medication:

Oral antiviral medication/protease inhibitor

Mechanism of action[1]:

Paxlovid combines Nirmatrelvir, a new medication, with Ritonavir, a known antiviral. Nirmatrelvir is a novel protease inhibitor which works to block the activity of an enzyme that the SARS-CoV-2 virus needs in order to replicate/reproduce. In studies, this drug is given with Ritonavir, a medication often used in treatment of HIV; a known inhibitor of cytochrome P450-3A4, an enzyme that degrades protease inhibitors, to help slow the metabolism of the Nirmatrelvir molecule.

Efficacy:

The EPIC-HR trial demonstrated that starting ritonavir-boosted nirmatrelvir treatment in nonhospitalized adults with mild to moderate COVID-19 within 5 days of symptom onset reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo.[2]

Current Dosing Guidance for Paxlovid:
FDA emergency use authorization was granted December 22, 2021 at a dose of 300mg (two 150mg tablets) of nirmatrelvir with one 100mg tablet of ritonavir, given twice daily for five days.

[1] PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets) For Patients
[2] Pfizer's Novel COVID-19 Oral Antiviral Treatment Candidate Reduced Risk of Hospitalization or Death by 89% in Interim Analysis of Phase 2/3 EPIC-HR Study | Pfizer

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Dose Adjustments:

Renal impairment reduces the clearance of nirmatrelvir. In patients with suspected renal impairment, clinicians may consider checking the patient's renal function to inform the dosing of ritonavir-boosted nirmatrelvir. The dose should be reduced to nirmatrelvir 150 mg with ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥30 to <60 mL/min). Ritonavir-boosted nirmatrelvir **is not recommended** in patients with an eGFR of <30 mL/min until more data are available.

INDICATIONS for Paxlovid (under FDA EUA):

- Treatment of mild-to-moderate COVID-19 in adults and pediatric patients.
- Aged 12 years and older, and weighing at least 40 kilograms (~ 88 pounds).
- Positive results of direct SARS-CoV-2 testing, and at high risk for progression to severe COVID-19, including hospitalization or death.
- Paxlovid should be initiated as soon as possible after diagnosis of COVID-19 and within five days of symptom onset.

Common side-effects

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea, hypertension, and myalgia.

Case reports have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir. Case reports and results from the EPIC-HR trial also describe instances of increases in SARS-CoV-2 RNA levels following completion of the treatment course.[3] The frequency, mechanism, and clinical implications of these events are not yet known. There are currently no data on the efficacy of administering longer courses or a second course of ritonavir-boosted nirmatrelvir.

Drug-Drug Interactions[4]

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. Boosting with ritonavir, which is a strong CYP3A inhibitor and a P-glycoprotein inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, it may also increase concentrations of certain concomitant medications, thereby increasing the potential for serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters. Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19, drug-drug interactions that can be safely managed should not preclude the use of this medication.

[3] Ritonavir-Boosted Nirmatrelvir (Paxlovid) | COVID-19 Treatment Guidelines (nih.gov)
[4] Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)

Before prescribing ritonavir-boosted nirmatrelvir, carefully review the patient's concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs. Consult a quick reference list or a drug interactions website for more guidance on management of each concomitant medication. Some quick reference tables from the NIH are at the end of this document, and available here:

Please also refer to Table B from the COVID-19 Test-to-Treat Outpatient Therapy Algorithm.

Further reading:

https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-3-0/

https://www.fda.gov/media/155050/download

CONTRAINDICATIONS for Paxlovid (under FDA EUA):

- Age <12
- Advanced kidney disease (GFR <30 mL/min)
- Advanced liver disease
- Severe COVID-19 illness requiring hospitalization
- Aged 12 years and older, and weighing at least 40 kilograms (~ 88 pounds).
- Positive results of direct SARS-CoV-2 testing, and at high risk for progression to severe COVID-19, including hospitalization or death.
- Paxlovid should be initiated as soon as possible after diagnosis of COVID-19 and within five days of

RISE Project Overview

Reaching Impact, Saturation, and Epidemic Control (RISE) is a 5-year global project funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Agency for International Development (USAID) which works with countries to achieve a shared vision of attaining and maintaining epidemic control, with stronger local partners capable of managing and achieving results through sustainable, self-reliant, and resilient health systems by 2024.

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