RECOVERY
Randomised Evaluation of COVID-19 Therapy

Paxlovid

Intervention

Paxlovid 300/100 (two nirmatrelvir 150mg tablets plus one ritonavir 100mg tablet) twice daily for 5 days, with the course completed at home if discharged.

Summary of information on Paxlovid in COVID-19

Paxlovid is a combination of nirmatrelvir (PF-07321332) and ritonavir. Nirmatrelvir is a 3-chymotrypsin-like protease inhibitor which inhibits cleavage of polyproteins involved in viral replication.[1] It is co-packaged with ritonavir which inhibits CYP3A-dependent metabolism and hence increases the concentration of nirmatrelvir. It is approved in the UK for the treatment of adults with COVID-19 who do not require supplemental oxygen and are at increased risk of progression to severe disease.[2]

In the EPIC-HR trial, 2085 non-hospitalised patients with COVID-19 and symptom onset ≤5 days ago were randomised to receive Paxlovid (300/100 mg) or placebo twice daily for 5 days.[3] Among all participants, 8/1039 (1%) allocated Paxlovid vs 66/1046 (6%) allocated placebo had COVID-19 related hospitalisation or died within 28 days, a reduction of 88%. Rates of adverse events were similar between the two groups, leading to discontinuation of treatment in 2% taking Paxlovid and 4% taking placebo. Paxlovid has not been assessed in hospitalised patients with COVID-19.

Potential harm

The summary of product characteristics lists the following adverse reactions:

- Altered taste (6% in EPIC-HR), diarrhoea (3%), vomiting (1%)
- Hepatitis and jaundice have occurred in patients receiving ritonavir
- Ritonavir has the potential to interact with other drugs, as below

Frequently asked questions

1. What are the contraindications to Paxlovid?

Contraindications:

- Age <18 years
- First trimester of pregnancy (<12 weeks)
- Severe hepatic impairment (Child-Pugh class C)
- Severe renal impairment (eGFR <30 mL/min/1.73m^2)
- Known hypersensitivity to nirmatrelvir or ritonavir
- Inability to swallow tablets (no NG or IV formulations are available)
- Use of Paxlovid during the current illness
- Concomitant therapy with drugs that are highly dependent on CYP3A for clearance and which could be associated with serious reactions.*

*There are many drugs that can interact with ritonavir, use the University of Liverpool COVID-19 interaction checker to identify potentially harmful interactions: https://www.covid19-druginteractions.org/prescribing_resources/paxlovid-patient-assessment). Refer to the protocol appendix and SPC for specific drugs not listed on the Liverpool website, or if the website is unavailable.

2. What are reasons for caution when giving Paxolvid?

- Women of child-bearing potential should be advised not to get pregnant while taking Paxlovid. Since ritonavir may decrease the efficacy of oral contraceptives, women using combined oral contraceptives should be advised to use effective alternative contraception or an additional barrier method until after one complete menstrual cycle after stopping.
- The necessity of using of other drugs metabolised by CYP3A (or which induce or inhibit CYP3A) should be reviewed. It may be appropriate to temporarily withhold such drugs while receiving Paxlovid or consider alternatives. This should be decided by the clinical team, aided by the Liverpool interaction checker above.
- Patients with abnormal liver function should be monitored.

3. Does Paxolvid need dose adjustment in mild renal impairment?

Patients with moderate renal impairment (eGFR ≥30 <60 mL/min/1.73m^2) should receive 150/100 mg twice daily (i.e. one nirmatrelvir 150mg tablet and one ritonavir 100mg tablet). Patients with more severe renal impairment (eGFR <30 mL/min/1.73m^2) are not eligible for the Paxlovid comparison.

4. Can Paxlovid be given along with corticosteroids?

Paxlovid can be given with dexamethasone at standard doses used in the treatment of COVID-19 (6mg daily). Because of the potential for Paxlovid to increase plasma concentrations of dexamethasone, it should not be used in patients taking significantly higher-doses, and for this reason patients cannot simultaneously be entered into the Paxlovid and high-dose dexamethasone comparisons in RECOVERY. Interactions with prednisolone are unlikely to be clinically significant.[4]

5. Can patients receiving other COVID-19 treatments be recruited into the Paxlovid comparison?

Yes, other than high-dose dexamethasone as mentioned above, Paxlovid has no interactions with any current standard COVID-19 therapies or those being studied in RECOVERY (i.e. tocilizumab, baricitinib, remdesivir, molnupiravir, sotrovimab, casirivimab/imdevimab, or empagliflozin).

6. Can Paxlovid be given to women in the 2nd and 3rd trimester, or to breast-feeding women?

These women are potentially eligible after discussion of risks and benefits. Note that from April 2022 enrolment of any pregnant woman into RECOVERY will need to involve a documented discussion with a consultant obstetrician or obstetric physician. Their consent discussion must be documented in their medical records (and a copy of this discussion will be requested by the coordinating centre). See details in protocol appendix and on Site Teams page of the website.

7. Can patients who have already received Paxlovid be recruited into the Paxlovid comparison in RECOVERY?

No. If they received any doses of Paxlovid during this illness they should not be included in this comparison.

8. Can Paxlovid be given intravenously or via an enteral feeding tube?

No. The tablets should be swallowed whole and not chewed, broken or crushed.

9. If participants are discharged before completing the course, should they complete it at home?

Yes. They should be provided with the remainder of their course to complete at home. For patients with moderate renal impairment (eGFR ≥30 <60 mL/min/1.73m^2), the unnecessary nirmatrelvir tablets should be removed from the packaging by hospital staff before providing it to the patient to take home.

References

1. Owen, D. R. *et al.* An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. *Science* **374**, 1586–1593 (2021)
2. Paxlovid 150 mg/100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc). www.medicines.org.uk/emc/product/13145
3. Hammond, J. *et al.* Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med* (2022) doi:10.1056/NEJMoa2118542
4. Liverpool COVID-19 Interactions. www.covid19-druginteractions.org