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Two new oral antivirals for covid-19: ▼ molnupiravir and ▼ nirmatrelvir plus ritonavir

What you need to know

- ▶ Molnupiravir and nirmatrelvir plus ritonavir have been licensed by the Medicines and Healthcare products Regulatory Agency for the treatment of covid-19 in adults.
- ▶ Evidence of clinical efficacy for each drug is based on interim analysis of data from a single placebo-controlled trial in unvaccinated adults.
- ▶ Both trials recruited non-hospitalised adults with mild-to-moderate covid-19 who had at least one risk factor for severe covid-19 illness.
- ▶ The risk of hospitalisation or death was reduced when molnupiravir (NNT 33) or nirmatrelvir plus ritonavir (NNT 18) was started within 5 days of onset of covid-19 symptoms.
- ▶ Common adverse effects with molnupiravir include diarrhoea, nausea and dizziness.
- ▶ Common adverse effects with nirmatrelvir plus ritonavir include dysgeusia, diarrhoea and vomiting.
- ▶ Nirmatrelvir plus ritonavir has an extensive list of possible serious and life-threatening drug interactions.

Introduction

In the UK, since the start of the covid-19 pandemic in 2019, there have been over 165 000 deaths within 28 days of a positive test and over 185 000 deaths in which covid-19 was listed on the death certificate.¹ A successful programme of vaccination against SARS-CoV-2 has delivered over 140 million doses since being introduced in December 2020.² Nevertheless, covid-19 continues to cause serious illness, hospitalisation and death. A parallel strategy to the introduction of vaccines against covid-19 has been the development of antiviral drugs to treat people who have been infected with SARS-CoV-2. Two oral antiviral products have been authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of covid-19 in adults.^{3,4} Here, we provide an overview of both drugs.

▼ Molnupiravir

Brand name: Lagevrio
Formulation: 200 mg hard capsules
Market Authorisation Holder: Merck Sharp & Dohme (UK) Limited
Indication: treatment of mild to moderate covid-19 in adults with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness
Dose: 800 mg every 12 hours for 5 days
Cost: no price available
Classification: Prescription only medicine (POM) subject to additional monitoring (▼).

About molnupiravir

Molnupiravir is a prodrug that undergoes conversion in the plasma before being phosphorylated in cells to its active form.^{5,6} The active form competes for virally encoded RNA-dependent RNA polymerase and produces its antiviral effect by a process known as viral error catastrophe. This is thought to increase viral mutation rate beyond a biologically tolerable threshold leading

to the accumulation of errors in the viral genome that inhibits replication.^{5,6}

Efficacy and safety data

Evidence for the efficacy and safety of molnupiravir comes from the MOVE-OUT study, which recruited non-hospitalised adults who had not been vaccinated against covid-19 and who had mild-to-moderate symptoms of covid-19 that had started within the previous 5 days and laboratory-confirmed SARS-CoV-2 infection no more than 5 days earlier.⁷ In addition, participants had to have at least one risk factor for development of severe covid-19 illness (eg, age >60 years; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; obesity; serious heart conditions; diabetes mellitus). Exclusion criteria included an anticipated need for hospitalisation for covid-19 within the next 48 hours; dialysis or estimated glomerular filtration rate less than 30 mL/min/1.73 m²; pregnancy; unwillingness to use contraception during the intervention period and for at least 4 days after completion of the regimen; severe neutropenia; platelet count below 100 000/ μ L; and SARS-CoV-2 vaccination.⁷ Participants were randomised to treatment with either oral molnupiravir 800 mg twice daily or matching placebo for 5 days. Use of antipyretic agents, anti-inflammatory agents or glucocorticoids was allowed. The primary outcome was the incidence of hospitalisation (defined as ≥ 24 hours of acute care in a hospital) for any cause or death from any cause up to day 29.^{7,8} The trial was designed to recruit 1550 participants based on event rates of 6% with molnupiravir and 12% with placebo, and it was planned that an interim analysis would take place once 775 participants had been followed to day 29. Results from the study have been published in *The New England Journal of Medicine* (see box 1).⁷

Box 1 Publication information⁷

The MOVE-OUT study was supported by Merck Sharp and Dohme. The first draft of the MOVE-OUT study manuscript and editorial assistance was provided by employees of Merck Sharp and Dohme. Merck was listed as the affiliation for 14 of the MOVE-OUT study's authors.

Efficacy

The recorded baseline demographics of all randomised participants included 'white' (56%), 'American Indian/Alaska Native and white' (10%), 'American Indian/Alaska Native' (8%) and 'American Indian/Alaska Native, black/African American and white' (7%).⁹ The most frequently reported risk factors included obesity (74%), age >60 years (17%), diabetes (16%) and serious heart disease (12%). The three most common SARS-CoV-2 variants were delta (33%), mu (11%) and gamma (5%), with sequencing not available for 45%.⁹

The interim analysis included 775 participants (median age 44 years, 52% male) from 78 sites in 15 countries.⁹ In the modified intention-to-treat (mITT) analysis fewer people in the molnupiravir group were hospitalised or died than in the placebo group (7.3% vs 14.1%; absolute difference 6.8%, 95% CI -11.3 to -2.4; $p=0.001$) with a number-needed-to-treat (NNT) of 15.⁷

The full data set included 1433 participants (median age 45 years, 51% female) from 107 sites in 20 countries with 1408 people in the mITT analysis.⁷ Those who received molnupiravir had a lower risk of hospitalisation or death compared with placebo (6.8% vs 9.7%; absolute difference 3.0%; 95% CI -5.9 to -0.1; NNT 33). When the data were analysed for only covid-19-related hospitalisation or death, the event rate was 6.3% in the molnupiravir group and 9.2% in the placebo group (absolute difference 2.8%; 95% CI -5.7 to 0.0; NNT 36). The study's authors were not able to explain why the incidence of death/hospitalisation in the placebo group was much lower in the full analysis (9.7%) than in the interim analysis (14.1%). In the subgroups of people with diabetes and those who had SARS-CoV-2 nucleocapsid antibodies at baseline, the rate of hospitalisation or death was lower in those who received placebo than in those who received molnupiravir.⁷

Safety

The proportion of adverse events was similar in the two groups (30% in the molnupiravir group and 33% in the placebo group).⁷ There were also similar numbers of adverse events that were considered to be related to molnupiravir or placebo (8.0% vs 8.4%). Commonly reported events that occurred in $\geq 2\%$ of participants in the molnupiravir or the placebo group were covid-19 pneumonia (6.3% vs 9.6%), diarrhoea (2.3% vs 3.0%) and bacterial pneumonia (2.0% vs 1.6%).⁷ In the interim analysis of the MOVE-OUT study, the most common adverse reactions occurring in $\geq 1\%$ of subjects during treatment and during 14 days after the last dose were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were classified as mild or moderate.^{6,7}

Drug interactions

Based on the limited data, no drug interactions have been identified.⁶

Pregnancy and breast feeding

Molnupiravir is not recommended during pregnancy and women of childbearing potential should use effective contraception during treatment and for 4 days after the last dose of molnupiravir.⁶ Breast feeding is not recommended during treatment and for 4 days after the last dose of molnupiravir.⁶

Regulatory assessment

The MHRA granted molnupiravir conditional marketing authorisation in Great Britain and authorised supply in Northern Ireland under regulation 174 of the Human Medicines Regulations 2012.^{3,10} The MHRA's assessment of molnupiravir's efficacy and safety used interim data from the MOVE-OUT study.^{3,10} In its public assessment report, the MHRA noted that 'no conclusions can be drawn regarding expected differences in efficacy among

unvaccinated individuals or those who have generated antibodies due to natural infection (previous infection or recent infection) or due to vaccination against SARS-CoV-2 infection'.¹⁰ As part of the authorisation conditions attached to the approval of molnupiravir, the company is required to conduct a drug utilisation study, evaluate haematological adverse effects, and collect data on pregnancy outcomes for women exposed to molnupiravir in pregnancy.¹⁰

In the USA, the Food and Drug Administration (FDA) granted emergency use authorisation for molnupiravir for the treatment of mild-to-moderate covid-19 in adults with a positive result from direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe covid-19, and for whom alternative covid-19 treatment options authorised by the FDA are not accessible or clinically appropriate.¹¹ In relation to the evidence for use of molnupiravir in vaccinated people, the FDA's briefing document noted that 'while vaccinated individuals were excluded ... no treatment benefit was discernible among the small subgroup or participants who were seropositive (due to natural immunity) at baseline given the small number of events overall. However, there are numerous limitations to extrapolating findings from patients with natural immunity to those with vaccine-induced immunity'.¹²

Although the European Medicines Agency (EMA) has not authorised molnupiravir for use in the European Union (EU), it has issued advice to member states to support national regulators on its possible use before marketing authorisation has been granted.¹³ In its review the EMA commented 'the magnitude of benefit of molnupiravir documented in MK4482-002 [MOVE-OUT study] in unvaccinated and seronegative subjects is not expected to be applicable to a population comprising vaccinated and/or naturally primed seropositive subjects'. The EMA concluded that molnupiravir 'might provide clinical benefit for the treatment of confirmed covid-19 in adults who do not require supplemental oxygen and who are at increased risk of progression to severe covid-19'.¹⁴

▼ Nirmatrelvir plus ritonavir

Brand name: Paxlovid

Formulation: 150mg nirmatrelvir tablets co-packaged with 100mg ritonavir tablets

Market Authorisation Holder: Pfizer Limited

Indication: Treatment of covid-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe covid-19

Dose: 300 mg nirmatrelvir with 100 mg ritonavir taken together twice daily for 5 days, started as soon as possible after a positive SARS-CoV-2 test and within 5 days of onset of symptoms

Cost: no price available

Classification: Prescription only medicine (POM) subject to additional monitoring (▼).

About nirmatrelvir and ritonavir

The coronavirus 3-chymotrypsin-like protease (3CLpro) controls SARS-CoV replication and is important in the infection process.^{15,16} Nirmatrelvir is a peptidomimetic that inhibits SARS-CoV-2 3CLpro, which stops the protein processing polyprotein precursors and results in the prevention of viral replication.¹⁷ Paxlovid is a combination product that consists of 150 mg nirmatrelvir tablets and 100 mg ritonavir tablets. Ritonavir has no effect on SARS-CoV-2 but is used to inhibit cytochrome p450 (CYP3A) mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.¹⁷

Efficacy and safety data

Evidence for the efficacy and safety of nirmatrelvir plus ritonavir comes from a phase 2/3 randomised double-blind placebo-controlled study.^{17,18} The EPIC-HR study recruited unvaccinated non-hospitalised symptomatic adults (aged ≥ 18 years) with a confirmed diagnosis of SARS-CoV-2 infection within 5 days and who were at increased risk of progressing to severe illness.^{18–21} Risk factors included age ≥ 60 years, body mass index (BMI) >25 kg/m², current smoker, hypertension, diabetes and cancer.²¹ Exclusion criteria included moderate or severe renal impairment, pregnancy or breast feeding, SARS-CoV-2 vaccination or previous covid-19 infection and need for hospitalisation for the medical treatment of covid-19.¹⁹ Participants were randomised to receive nirmatrelvir plus ritonavir or placebo orally every 12 hours for 5 days.¹⁸ The primary outcome was the proportion of participants with covid-19-related hospitalisation or death from any cause at day 28. This was based on the mITT population whose treatment began within 3 days after the onset of signs and symptoms of covid-19 and excluded patients who had received or were expected to receive monoclonal antibody treatment. Secondary outcomes included incidence of adverse effects (up to day 34), duration and severity of covid-19 signs/symptoms (up to day 28) and proportion of participants who died (up to week 24).¹⁹ The study was designed to be able to show a 50% difference between the groups in covid-19 related hospitalisation or death from any cause (based on an anticipated rate of 7% in the placebo arm) of those who underwent treatment within 3 days of symptom onset.¹⁸ Results from the study have been published in *The New England Journal of Medicine* (see box 2).¹⁸

Efficacy

A total of 2246 people (mean age 46 years; 51% male) received either nirmatrelvir plus ritonavir (1120) or placebo (1126) and 2102 completed the safety follow-up on day 34.¹⁸ The baseline demographics of the participants were reported as 'white' (72%), 'Asian' (14%), 'American Indian or Alaska Native' (9%) and 'black' (5%). The most frequently reported risk factors were BMI ≥ 25 kg/m² (81%), smoking (39%) and hypertension (33%). The main SARS-CoV-2 variant was delta (98%).²¹

At the point of the interim data analysis in October 2021, 1361 participants had been randomised to receive either nirmatrelvir plus ritonavir or placebo and the mITT interim analysis included 774 people who took at least one dose within 3 days of onset of covid-19 symptoms.^{18–21} Fewer people in the nirmatrelvir plus ritonavir group were hospitalised or died than in the placebo group (0.77% vs 7.01%; absolute difference 6.3%, 95% CI -9.0 to -3.6 ; NNT 16).¹⁸ No deaths were reported in the nirmatrelvir plus ritonavir group compared with seven deaths in the placebo group.

Data from the final analysis included 1379 out of 2246 participants in the mITT population who took at least one dose within 3 days of onset of covid-19 symptoms.¹⁸ The estimated event rate of covid-19 hospitalisation or death from any cause at 28 days was lower with nirmatrelvir plus ritonavir compared with placebo (0.72% vs 6.53%; absolute difference 5.8%, 95% CI -7.8 to -3.8 ; NNT 17). There were no deaths in the nirmatrelvir plus ritonavir group and nine deaths in the placebo group.¹⁸

For patients who began treatment within 5 days after symptom onset, the rate of hospitalisation for covid-19 or death from any

cause at day 28 was 0.77% in the nirmatrelvir plus ritonavir group and 6.31% in the placebo group ($p < 0.001$; NNT 18).¹⁸

Safety

The incidence of adverse effects was similar with 23% experiencing adverse effects in the nirmatrelvir plus ritonavir group and 24% in the placebo group.¹⁸ The proportion of participants who discontinued treatment due to an adverse event was 2.1% in the nirmatrelvir plus ritonavir group and 4.2% in the placebo group. Adverse reactions that occurred in more than 1% of participants included dysgeusia (5.6% with nirmatrelvir plus ritonavir vs 0.3% with placebo), diarrhoea (3.1% vs 1.6%), headache (1.4% vs 1.3%) and vomiting (1.1% vs 0.8%).¹⁸

Drug interactions

The summary of product characteristics (SPC) includes an extensive list of possible drug interactions.¹⁷ Nirmatrelvir plus ritonavir inhibits CYP3A and may increase plasma concentrations of drugs that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when coadministered with nirmatrelvir plus ritonavir. The SPC includes a table of medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events and are contraindicated for concomitant use with nirmatrelvir plus ritonavir (eg, amiodarone, clozapine, colchicine, diazepam, fusidic acid, simvastatin and pethidine).¹⁷ Products that induce the metabolism of nirmatrelvir plus ritonavir 'where significantly reduced plasma nirmatrelvir/ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance' are also contraindicated (eg, carbamazepine, phenytoin, rifampicin and St John's Wort).¹⁷

Ritonavir may also inhibit P-glycoprotein pathways and can induce activity of other enzymes (eg, CYP1A2, CYP2C8, CYP2C9 and CYP2C19).¹⁷

Careful assessment of a patient's medicines (including over-the-counter, herbal and recreational drugs) is needed.²² The University of Liverpool has produced an interaction checking tool for covid-19 drug interactions (<https://www.covid19-druginteractions.org/checker>). In some cases, it may be necessary to consider an alternative treatment for covid-19.²²

Contraindications

In addition to the contraindication for drug interactions, nirmatrelvir plus ritonavir is contraindicated in people with severe hepatic impairment or severe renal impairment.¹⁷

Pregnancy and breast feeding

The SPC states that women of childbearing potential should avoid becoming pregnant during treatment with nirmatrelvir plus ritonavir.¹⁷ Breast feeding should be stopped during treatment with nirmatrelvir plus ritonavir and for 7 days after the last dose.

Regulatory assessment

The MHRA granted nirmatrelvir plus ritonavir conditional marketing authorisation in Great Britain and authorised supply in Northern Ireland under regulation 174 of the Human Medicines Regulations 2012. The MHRA approval process used interim data from the EPIC-HR study.^{4,20} The MHRA noted that some important limitations in using the clinical data need to be taken into account and these include 'uncertainty in relation to circulating SARS-CoV-2 variants, and the generalisability of the treatment benefit to a largely vaccinated public'.²⁰

Box 2 Publication information¹⁸

The EPIC-HR study was supported by Pfizer. The first draft of the EPIC-HR study manuscript was provided by employees of a contract research organisation funded by Pfizer. Pfizer was listed as the affiliation for 11 of the EPIC-HR study's authors.

The US FDA issued emergency use authorisation for nirmatrelvir plus ritonavir for the treatment of 'mild-to-moderate coronavirus disease (covid-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms or about 88 pounds) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe covid-19, including hospitalization or death'.²³

The EMA granted conditional marketing authorisation for nirmatrelvir plus ritonavir for use in the EU for the treatment of covid-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe covid-19.²⁴ The EMA noted that 'the complexity of the interaction profile driven by the ritonavir booster dose could be a limiting factor in its use'.²⁵

Uncertainties over the evidence

Concerns have been expressed over regulatory decisions to approve molnupiravir.²⁶ These include issues relating to the use of press releases to publicise trial findings, the difference between the interim and final results, and the clinical significance of the findings (including some of the subgroup analyses).^{26,27} In addition, the clinical trials involving molnupiravir and nirmatrelvir plus ritonavir did not include patients who had been vaccinated against SAR-CoV-2. Furthermore, there is a lack of clarity over the cost of treatment and a paucity of published cost-effectiveness data on the use of either drug in the management of covid-19.²⁶

National guidance

The UK has issued eligibility criteria for drug treatment for non-hospitalised patients with symptomatic confirmed SARS-CoV-2 infection who are showing no signs of clinical recovery and who are at the highest risk from covid-19.²⁸ It recommends nirmatrelvir plus ritonavir or the injectable monoclonal antibody ▼ sotrovimab as first-line choices, injectable ▼ remdesivir as second-line and molnupiravir as third-line. Specific guidance for nirmatrelvir plus ritonavir notes that it is not suitable for patients with a history of advanced decompensated liver cirrhosis, stage 4–5 chronic kidney disease, those receiving dialysis and for transplant patients due to interactions with immunosuppressive therapy. In addition, the guidance lists many contraindications because of other drug–drug interactions. The policy states that treatment with nirmatrelvir plus ritonavir or molnupiravir must be started within 5 days of symptom onset.²⁸

Ongoing research

In the UK, the PANORAMIC study is a 'platform randomised trial of antiviral therapeutic agents for use by clinically vulnerable people in the community with confirmed acute symptomatic SARS-CoV-2 infection'.²⁹ The trial will assess the effect of an antiviral agent plus usual care against usual care on the primary outcome of all-cause non-elective hospitalisation and/or death within 28 days of randomisation. It will recruit people with covid-19 symptoms within the previous 5 days, a positive PCR SARS-CoV-2 test and who are aged ≥50 years or aged 18–49 years with an underlying health condition that is considered to make them clinically vulnerable. Molnupiravir is the first oral antiviral to be included in the trial. Recruitment to the trial is encouraged for patients who are not eligible for treatment under the national policy.²⁸

What other drug bulletins say

Australian Prescriber noted that molnupiravir's benefit in treating vaccine breakthrough infections is not known and that the safety and efficacy of nirmatrelvir plus ritonavir in vaccinated people have yet to be established.^{30,31}

Prescrire International concluded that "the value of molnupiravir as an early treatment for mild or moderate covid-19 is not demonstrated, including in unvaccinated patients at increased risk of progression to serious disease."³²

The Medical Letter recommended that molnupiravir "should be reserved for nonpregnant, adult outpatients for whom alternative treatment options are not available or clinically appropriate. If Paxlovid is available, it should generally be tried first."³³

Conclusion

▼ Molnupiravir and ▼ nirmatrelvir plus ritonavir are oral antiviral agents that have been licensed for the treatment of mild to moderate covid-19 in adults with a positive SARS-CoV-2 diagnostic test and who are at risk of developing severe illness. In the UK, the MHRA's decision to licence both drugs was based on interim analysis of data from a single placebo-controlled trial of the effect of each agent on hospitalisation and death.

For molnupiravir, the full analysis showed that the incidence of hospitalisation or death in unvaccinated people treated within 5 days of symptom onset was 6.8% compared with 9.7% with placebo (NNT 33). For nirmatrelvir plus ritonavir, the incidence of hospitalisation or death was 0.8% compared with 6.3% for placebo (NNT 18) for unvaccinated people treated within 5 days of symptom onset. Although indirect evidence appears to suggest that nirmatrelvir plus ritonavir may be more effective than molnupiravir, its use is complicated by an extensive list of potentially serious drug interactions.

There are several limitations to the evidence for molnupiravir and nirmatrelvir plus ritonavir that need to be taken into consideration. The licensing decisions were based on interim results from a small number of people who were treated with these antiviral agents. It is also worth noting that trial participants in both studies had not been vaccinated against SARS-CoV-2 and the efficacy of these antivirals in a population in which a high proportion of people have been vaccinated against SARS-CoV-2 is not known. We also do not know how effective molnupiravir and nirmatrelvir plus ritonavir will be against new variants of SARS-CoV-2, and whether resistance to these antivirals will develop. At this stage there is very limited information on adverse effects.

Given the severe global impact of covid-19, research and development of drugs and vaccines to tackle the disease is welcome. However, it should be noted that licensing decisions for these two oral antiviral agents have been based on the interim results of two studies involving small numbers of patients. Furthermore, public access to the summary data on safety and efficacy of these drugs has been slow and much of the clinical information has been issued in the form of press releases. We believe that greater scrutiny of the full data from the clinical trials is needed and that further studies are required to provide a more accurate assessment of the efficacy and safety of these drugs. We are also concerned that the cost of these drugs to the health service has not been made public and that no health economic analyses have been published to support their introduction.

Competing interests None declared.

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