NEW DRUGS

Nirmatrelvir and ritonavir

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Approved indication: COVID-19

Paxlovid (Pfizer)
nirmatrelvir 150 mg film-coated tablets, ritonavir 100 mg film-coated tablets

Viral proteases are feasible targets for antiviral drugs. The main protease of SARS-CoV-2 plays a pivotal role in viral replication so inhibiting it could be an effective treatment for COVID-19. The antiviral drug nirmatrelvir, given with ritonavir, has been provisionally approved for the treatment of COVID-19 in adults who have an elevated risk of progressing to hospitalisation or death but do not require supplemental oxygen. This approval is based on incomplete data and may be revised with the publication of peer-reviewed results. The efficacy of the combination against the Omicron variant is not yet established. The combination is not approved for patients requiring hospitalisation for severe or critical COVID-19.

Nirmatrelvir works by binding to the SARS-CoV-2 3CL protease to prevent viral replication. To boost plasma concentrations, it is taken with ritonavir, an inhibitor of cytochrome P450 (CYP) 3A4 that blocks the metabolism of nirmatrelvir. Ritonavir itself is inactive against SARS-CoV-2.

The recommended regimen is two nirmatrelvir 150 mg tablets and one ritonavir 100 mg tablet taken together every 12 hours for five days, starting as soon as possible after a diagnosis of COVID-19 and within five days of the onset of symptoms. The tablets should be swallowed whole, with or without food, and not chewed, broken or crushed. As its metabolism by CYP3A4 is blocked by ritonavir, nirmatrelvir is mainly excreted unchanged in the urine and faeces. The mean half-life of nirmatrelvir with ritonavir is about seven hours. In patients with moderate renal impairment, a reduced dose of nirmatrelvir is recommended, but this adjusted regimen has not been clinically tested. The combination is contraindicated in patients with severe renal or hepatic impairment.

Nirmatrelvir and ritonavir are also contraindicated in patients who are taking drugs that are highly metabolised by CYP3A and drugs that are strong CYP3A inducers. There are many potential drug interactions.

A phase II/III double-blind, randomised controlled trial investigated the efficacy of the combination in unvaccinated patients at high risk of hospitalisation or death. This trial enrolled 2246 adults with COVID-19, mainly (98%) the Delta variant. Among those who were treated within three days of symptom onset, 0.7% (5/697) of the patients in the treatment group and 6.5% (44/682) of the placebo group were hospitalised within 28 days following randomisation. There were no deaths in the treatment group whereas nine patients in the placebo group died. When treated within five days of symptom onset, 0.8% (8/1039) of the treatment group and 6.3% (66/1046) of the placebo group were hospitalised within 28 days following randomisation. There were no deaths in the treatment group whereas 12 patients in the placebo group died.[1]

In this trial, up to 34 days after the last dose, 22.6% (251/1109) of the patients in the treatment group and 23.9% (266/1115) of the patients in the placebo group experienced treatment-emergent adverse reactions, which were usually mild in intensity. The most common adverse reactions were dysgeusia, diarrhoea, headache and vomiting. Nine (0.8%) patients in the treatment group and seven (0.6%) patients in the placebo group discontinued treatment due to an adverse event considered to be related to the drug or placebo.[1]

The safety and efficacy of nirmatrelvir and ritonavir in children and pregnant women are unknown. Breastfeeding should be discontinued during and for seven days after treatment. Ritonavir is likely to reduce the efficacy of combined hormonal contraceptives, so women are advised to use additional or alternative contraceptives during treatment and during a menstrual cycle after treatment.

Nirmatrelvir boosted with ritonavir should be used with caution for COVID-19 because of the potential for drug–drug interactions. The safety and efficacy of this treatment in vaccinated people have yet to be established.

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REFERENCES

1. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al.; EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. New Engl J Med 2022 [Epub 2022 Feb 16]. https://doi.org/10.1056/NEJMoa2118542

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.