In brief

Paxlovid

26 September 2022

Summary

- Paxlovid (PF-07321332/ ritonavir) is an oral antiviral medicine that contains nirmatrelvir tablets co-packaged with ritonavir tablets.[1]
- In clinical trials, Paxlovid treatment was effective and beneficial in non-hospitalised and unvaccinated patients with COVID-19, who are at a high risk of disease progression and infected during the pre-Omicron period of the COVID-19 pandemic.[2] However, it did not have a significant clinical benefit in people with a standard risk.[3]
- Two real-world studies from the Omicron-predominant period reported that Paxlovid treatment reduced the risk of disease progression (death or hospitalisation) in patients aged 65 or older.[4, 5] Both the studies found no clinical benefit of treatment in patients aged under 65.[4, 5] One study found no clinical benefit of Paxlovid treatment among fully vaccinated patients with regards to progression to severe disease, while the other found evidence of benefits regardless of vaccination or prior infection history in older adults.[4, 5]
- Paxlovid was associated with a faster time to viral clearance in high-risk patients.[6-8]
- While COVID-19 rebound (resurgence of detectable virus or symptoms after initial recovery) has been reported in patients treated with Paxlovid, hospital admissions and emergency department encounter due to rebound is rare (fewer than 1% of patients).[9] COVID-19 rebound is also reported among untreated patients.[10, 11]

Regulatory context: Australia

- 1 May 2022: Paxlovid was listed on the Pharmaceutical Benefits Scheme.[12]
- 18 January 2022: Paxlovid was granted provisional approval by the Therapeutic Goods Administration (TGA).[1]

Regulatory context: International

- 06 July 2022: The U.S. Food and Drug Administration authorised pharmacists to prescribe Paxlovid with certain limitations.[13]
- 17 January 2022: Health Canada authorised Paxlovid for patients with mild to moderate COVID-19 at high risk of developing serious disease.[14]
- 31 December 2021: Medicines and Healthcare products Regulatory Agency (MHRA), UK approved Paxlovid for people with mild to moderate COVID-19 who are at high risk of developing severe COVID-19.[15]
- 22 December 2021: U.S. Food & Drug Administration authorised Paxlovid for treatment of COVID-19.[16]

Effectiveness

- August 2022: In a real-world study from Israel (Omicron period), treatment with nirmatrelvir was associated with a significantly lower risk of death due to Covid-19 (hazard ratio: 0.21) and hospitalisation hospitalization due to Covid-19 (hazard ratio: 0.27) among patients 65 years of age or older and who were at high risk for progression to severe disease. This was the case regardless of whether a patient had previous SARS-CoV-2 immunity from vaccination or infection. No evidence of benefit was found in younger adults.
    - Crude incidence rate per 10,000 person-days for the outcomes in the nirmatrelvir group versus control among patients aged 65 or older for hospitalisation: 14.7 versus 58.9.[4]
- August 2022: In a real-world study from Hong Kong (Omicron BA.2 period), treatment with Paxlovid in patients with COVID-19, who did not require supplemental oxygen on admission to hospital, was associated with a significantly lower risk of all-cause mortality (hazard ratio: 0.34); disease progression (hazard ratio: 0.57) and the need for oxygen therapy (hazard ratio: 0.73).
    - Crude incidence rate per 10,000 person-days for the outcomes in the Paxlovid group versus control:
        - All-cause mortality: 10.28 versus 26.47
        - Invasive mechanical ventilation: 1.93 versus 1.73
        - Intensive care unit admission: 0.00 versus 0.29
        - Need for oxygen therapy: 31.53 versus 38.24
        - Composite disease progression outcome: 35.04 versus 54.98
    - According to subgroup analysis, treatment with Paxlovid did not have a significant benefit with regards to all-cause mortality, invasive mechanical ventilation, need for oxygen therapy, and composite progression outcome among patients aged 65 or under, or those who are fully vaccinated.[5]
- August 2022: In a real-world study from the United States (Omicron period), treatment with Paxlovid with associated with improved outcomes among non-hospitalised vaccinated patients. At 30-days follow-up and treatment versus control:
    - All-cause Emergency Room visit: 7.34% versus 12.5%; absolute risk reduction: 5.16%
    - All-cause hospitalisation: 0.8% versus 2%; absolute risk reduction: 1.2%
    - 30-day mortality: 0% versus 0.8%: absolute risk reduction: 0.8%
    - Significantly fewer multisystem symptom burden and subsequent complications such as lower respiratory tract infection, cardiac arrhythmia, and diagnostic radiology testing in the treatment group.[17]
- August 2022: Older patients (aged 60 years or older) who were treated with Paxlovid during Omicron-predominant period were significantly more likely to have a viral clearance within nine days of first positive test than patients who did not receive Paxlovid treatment (62.25% versus 54.03%, p=0.003).[6] Paxlovid treatment within five days of diagnosis in immunocompromised and hospitalised patients was associated with faster viral clearance compared to treatment after five days of diagnosis.[7]
- August 2022: An in-vitro study suggests that nirmatrelvir remains susceptible to Omicron subvariants BA.2.12.1, BA.4 and BA.5 at a similar level to that of the ancestral strain.[18]
- July 2022: A meta-analysis based on two randomised clinical trials (EPIC-HR and EPIC-SR) (publications up to April 2022) reported that Paxlovid reduced the risk of mortality (11.7 fewer

deaths per 1000) and hospitalisation (46.2 fewer hospitalisation per 1000). The relative risk reduction for mortality was 88%. Treatment with Paxlovid did not led to an increase in adverse events.[19]

- June 2022: Preliminary results from the EPIC-SR trial (phase 2–3 double-blind, randomised, controlled trial, patients enrolled through December 2021), which evaluated the use of Paxlovid in patients who are at standard risk for developing severe COVID-19, reported a non-statistically significant risk reduction of 51% (treatment arm: 5/576; placebo: 10/569) for progression to severe COVID-19.
    - In vaccinated patients with at least one risk factor for severe COVID-19, non-significant 57% reduction in hospitalisations and death observed.[3]
- June 2022: In a non-controlled, real-world, population-based study from Israel (Omicron period), Paxlovid was associated with a significant decrease in the rate of severe COVID-19 or mortality with an adjusted hazard ratio of 0.54.
    - The study concluded that Paxlovid appears to be more effective in older patients, immunosuppressed patients, and patients with underlying neurological or cardiovascular disease (interaction P <0.05 for all).[2]
- April 2022 :The EPIC-HR trial (phase 2–3 double-blind, randomized, controlled trial, pre-Omicron) found that, in symptomatic, unvaccinated, high-risk, and non-hospitalised adults with mild-to-moderate COVID-19, oral Paxlovid reduced the risk of hospitalisation or death by approximately 88.9% when treated within three days of symptom onset. At day 28 following symptom onset:
    - 0.72% of patients (10 out of 697) who received nirmatrelvir plus ritonavir were either hospitalised (n=5) or died (n=0)
    - 6.53% of patients (44 out of 682) who received placebo were either hospitalised (n=44) or died (n=9)[20]

Safety

- April 2022: In the EPIC-HR trial, the incidence of any adverse event was similar between the nirmatrelvir plus ritonavir and placebo groups (22.6% versus 23.9%).[20]

COVID-19 rebound after treatment.

- COVID-19 rebound refers to a resurgence in viral level or symptoms after initial recovery, and usually occurs within two to eight days.[21]
- August 2022: Among patients who were not treated with Paxlovid or other drugs, the viral rebound and symptom rebound rates at day 8 post symptom onset were 12% and 27%, respectively. Around 2% patients experienced both viral and symptom rebound.[11]
- August 2022: In a small sample pre-print study, 27% of individuals (3 out of 11) treated with Paxlovid had a virologic rebound, compared to 4% (1 out of 25) in the untreated group. For those that did not rebound, Paxlovid significantly reduced time to negative test result after the infection.[8]
- June 2022: A real-world study based on electronic health records found that COVID-19–related hospital admissions and emergency department encounters five to 15 days after Paxlovid treatment was rare, with a rate of 0.11% and 0.74% respectively.[9]

- June 2022: A retrospective cohort study of electronic health records (pre-print) of 11,270 patients who took Paxlovid within five days of their COVID-19 infection during the Omicron-predominant period, reported rebound rates at seven days and 30 days after the last day of treatment as:
    - COVID-19 infection: 3.53% and 5.40%
    - COVID-19 symptoms: 2.31% and 5.87%
    - COVID-19 hospitalisation: 0.44% and 0.77%
    - Patients with COVID-19 rebound had significantly higher prevalence of underlying medical conditions than those without.[22]
- May 2022: The United States Centers for Disease Control and Prevention (CDC) notes that "a brief return of symptoms may be part of the natural history of SARS-CoV-2 infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status".[21]

Dosage

- The TGA recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets), with 100 mg ritonavir (one100 mg tablet), taken together orally every 12 hours for 5 days.

Methods

To inform this brief, PubMed and Google searches were conducted using terms related to Paxlovid on the 31 August 2022.

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