Technology Guidance

Nirmatrelvir and ritonavir combination

for treating mild-to-moderate COVID-19

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Nirmatrelvir 150 mg tablet and ritonavir 100 mg tablet combination for treating mild-to-moderate Coronavirus Disease 2019 (COVID-19) in patients aged 18 years or older who are immunocompromised.

Funding status

Nirmatrelvir 150 mg tablet and ritonavir 100 mg tablet combination is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 November 2024.

Nirmatrelvir and ritonavir combination should be used in line with the additional clinical criteria listed in the Annex.

Updated: 1 April 2026

Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the July 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of nirmatrelvir and ritonavir combination as an oral antiviral treatment for mild-to-moderate Coronavirus Disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalisation or death. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions. Clinical and economic evidence for nirmatrelvir and ritonavir combination was considered in line with its registered indication.

1.2. The use of molnupiravir, another oral antiviral treatment for mild-to-moderate COVID-19, was outside the scope of the evaluation as molnupiravir had not achieved full product registration with the Singapore Health Sciences Authority (HSA) at the time of evaluation.

1.3. The evidence for nirmatrelvir and ritonavir combination was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1 According to local published treatment guidelines, most patients with mild-to-moderate COVID-19 who are up to date with COVID-19 vaccinations typically require supportive care only, without the need for specific treatment interventions.

2.2 However, certain subgroups of patients have an increased risk for progression to severe COVID-19 due to the presence of risk factors such as advanced age, or ongoing conditions or treatments that suppress the immune system. For these patients, treatment with nirmatrelvir and ritonavir combination may be considered within 5 days of COVID-19 symptom onset.

2.3 The Committee heard that nirmatrelvir and ritonavir combination has achieved full registration with the HSA for treating mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19. They also acknowledged the clinical need to consider funding for nirmatrelvir and ritonavir combination to improve treatment affordability.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence for nirmatrelvir and ritonavir combination from clinical trials and local observational data in adults with mild-to-moderate COVID-19 who were at high risk for progression to severe COVID-19.

3.2. The pivotal randomised trial (EPIC-HR) showed that, compared to placebo, nirmatrelvir and ritonavir combination reduced the risk of COVID-19-related hospitalisation or death from any cause in adults who had not received any COVID-19 vaccination. The Committee considered that the applicability of EPIC-HR trial results to the Singapore setting was uncertain. This was due to the differences in vaccination status between the trial and local populations, and the varying virulence of newer COVID-19 variants circulating locally.

3.3. The Committee noted that observational data were available from a large cohort of adults in Singapore with mild-to-moderate COVID-19, who were mostly fully vaccinated. Based on the data, nirmatrelvir and ritonavir combination treatment reduced the risk of hospitalisation or death compared with supportive care (without nirmatrelvir and ritonavir), albeit by a smaller extent than the treatment effect observed in EPIC-HR. The Committee acknowledged that the results were associated with uncertainty due to the lack of pre-specified analyses which could lead to bias.

3.4. Based on the available evidence, the Committee agreed that nirmatrelvir and ritonavir combination was superior in clinical effectiveness over placebo or supportive care, for treating adults who have mild-to-moderate COVID-19 and risk factors for progression to severe COVID-19.

3.5. In terms of safety, treatment-related adverse events were more commonly reported in the trials with nirmatrelvir and ritonavir combination, compared with placebo. These adverse events included dysgeusia and diarrhoea, which were mostly grade 1 or 2 non-serious events.

Cost effectiveness

4.1. The Committee reviewed a cost-effectiveness analysis conducted by ACE that compared nirmatrelvir and ritonavir combination treatment versus placebo or supportive care, in adults with mild-to-moderate COVID-19 who were at high risk for progression to severe COVID-19.

4.2. The Committee noted that, based on EPIC-HR trial data, the base-case incremental cost-effectiveness ratio (ICER) for nirmatrelvir and ritonavir combination was considered high and uncertain due to limitations in comparability of patient populations between the trial and local setting.

4.3. When local observational data from mostly fully vaccinated adults were applied in the economic model, the ICER for nirmatrelvir and ritonavir combination was unacceptably high (between SG$105,000 and SG$135,000 per quality-adjusted life year [QALY] gained) compared with supportive care. The Committee noted the ICER estimates were highly sensitive to the baseline risk of hospitalisation and death, and the relative treatment benefit from receiving nirmatrelvir and ritonavir combination compared to supportive care alone, which varied across different subgroups of patients.

4.4. Overall, based on the company's proposal, the Committee agreed that nirmatrelvir and ritonavir combination treatment may be considered an acceptable use of healthcare resources (ICER between SG$15,000 and SG$45,000 per QALY gained) for adults with mild-to-moderate COVID-19 who are immunocompromised in the local setting.

Estimated annual technology cost

5.1. The Committee noted the cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first year of listing nirmatrelvir and ritonavir combination on the MOH List of Subsidised Drugs for treating mild-to-moderate COVID-19 in adults who are immunocompromised.

5.2. The Committee acknowledged that the cost impact in subsequent years was uncertain as it would be impacted by the characteristics of future circulating COVID-19 variants, such as transmissibility and the severity of COVID-19 symptoms.

Recommendations

6.1. The Committee recommended nirmatrelvir 150 mg tablet and ritonavir 100 mg tablet combination be listed on the Medication Assistance Fund (MAF) for treating mild-to-moderate COVID-19 in patients aged 18 years or older who are immunocompromised. This decision was based on the clinical need, the totality of clinical evidence, and given that nirmatrelvir and ritonavir combination may be considered an acceptable use of healthcare resources for these patients.

6.2. The Committee also recommended nirmatrelvir and ritonavir combination be used in line with additional clinical criteria (listed in the Annex) to govern appropriate use in local practice.

ANNEX

MAF clinical criteria for nirmatrelvir and ritonavir combination

Treatment of mild-to-moderate Coronavirus Disease 2019 (COVID-19), within 5 days of symptom onset, in patients who are at high risk for progression to severe COVID-19, including hospitalisation or death, and who satisfy the requirements below:

(a) the patient has test-confirmed COVID-19 (PCR or antigen test positive); AND
(b) the patient does not have severe disease (e.g. hypoxia, SpO2 < 94%); AND
(c) the patient does not have any of the following contraindications to nirmatrelvir/ritonavir:
    (i) Significant drug-drug interactions that cannot be adjusted for; or
    (ii) Severe hepatic impairment (Child-Pugh Class C);

AND

(d) the patient is 18 years of age or older and is immunocompromised, where immunocompromised means the patient satisfies at least one of the following:
    (i) The patient is a transplant patient on medications that suppress the immune system, including solid organ and allogeneic stem cell transplants; or
    (ii) The patient is a cancer patient on active treatment with chemotherapy or other therapies that suppress the immune system; or
    (iii) The patient has one or more haematological cancers; or
    (iv) The patient has one or more non-cancer conditions that suppress the immune system; or
    (v) The patient has end-stage kidney disease (i.e. on haemodialysis or peritoneal dialysis); or
    (vi) The patient has advanced or untreated HIV.

VERSION HISTORY

Guidance on nirmatrelvir and ritonavir combination for treating mild-to-moderate COVID-19

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**
   Date of Publication 25 Oct 2024

2. **Annex updated to remove the contraindication for patients with glomerular filtration rate < 30 mL per minute, as reflected in the revised MAF clinical criteria**
   Date of Publication 1 April 2026