

**6.07 NIRMATRELVIR AND RITONAVIR,
Pack containing 4 tablets nirmatrelvir 150 mg and
2 tablets ritonavir 100 mg, 5
Paxlovid[®],
Pfizer Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 1 submission requested maintenance of the current General Schedule Authority Required (STREAMLINED) listing for the treatment of patients with mild to moderate Coronavirus disease (COVID-19) who are at high risk of severe disease requiring hospitalisation. Four high-risk populations are currently eligible to be prescribed nirmatrelvir and ritonavir under the Pharmaceutical Benefits Scheme (PBS):
- Persons aged ≥ 70 years
 - Persons aged ≥ 18 years who are moderately to severely immunocompromised or had previously required hospitalisation for COVID-19
 - Aboriginal and Torres Strait Islander persons aged ≥ 30 with ≥ 1 risk factor
 - Persons aged 50-69 years with ≥ 1 risk factor.
- 1.2 It is not clear that patients aged 50-69 years with only one additional risk factor should be considered to be at high risk of severe disease requiring hospitalisation. The PBAC recommended amendments of the restriction for nirmatrelvir and ritonavir at its out-of-session meetings in February 2023 and June 2023. In February 2023, the PBAC recommended amendments to permit PBS-reimbursed prescribing of nirmatrelvir and ritonavir for patients aged 60-69 year and one additional risk factor. In June 2023, the PBAC recommended further amendments permitting PBS-reimbursed prescribing of nirmatrelvir and ritonavir in patients aged 50-59 years with one additional risk factor. As detailed in paragraph 2.12, these amendments of the restriction for nirmatrelvir and ritonavir were intended to apply only on a temporary basis i.e., until the Commonwealth purchased stock was exhausted or had expired.
- 1.3 The sponsor also requested maintenance of the Prescriber bag listing of nirmatrelvir and ritonavir, for both Medical Practitioners and Nurse Practitioners, with the quantity being sufficient for two courses of nirmatrelvir and ritonavir. The submission stated that the Prescriber Bag listing remained necessary due to the urgency of commencing treatment as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset.
- 1.4 Continued listing was requested on the basis of cost-effectiveness analysis versus placebo (for no antiviral medication) and versus molnupiravir.

1.5 Table 1 summarises the key components of the research question addressed by the submission (as stated in the submission).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Four high-risk sub-populations defined by the current nirmatrelvir and ritonavir PBS listing: <ul style="list-style-type: none"> • Persons aged ≥70 years • Persons aged ≥18 years who are moderately to severely immunocompromised or had previously required hospitalisation for COVID-19 • Aboriginal and Torres Strait Islander persons aged ≥30 with ≥1 risk factor • Persons aged 50-69 years with ≥1 risk factor
Intervention	Paxlovid (2 x 150 mg nirmatrelvir tablets and 1 x 100 mg ritonavir tablet) taken together orally every 12 hours for 5 days
Main comparator	No SARS-CoV-2 antiviral medication (placebo)
Secondary comparator	Molnupiravir (Lagevrio®) The recommended dose of molnupiravir in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.
Outcomes	COVID related hospitalisations COVID related deaths Incidence of treatment-emergent adverse events (TEAEs) Incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuations
Clinical claim	The clinical claim for efficacy and safety is based on the primary outcomes of the EPIC-HR trial and supported by observational studies conducted in a highly vaccinated population during the Omicron era. <ul style="list-style-type: none"> • Nirmatrelvir/ritonavir is superior in terms of efficacy compared with placebo • Nirmatrelvir/ritonavir is similar in terms of safety compared with placebo

Source: Table 1.1.1, p4 of the submission.

2 Background

Registration status

2.1 Nirmatrelvir and ritonavir was granted provisional approval by the Therapeutic Goods Administration (TGA) on 20 January 2022 for the treatment of coronavirus disease 2019 (COVID-19) in adults 18 years of age and older, who do not require initiation of supplemental oxygen due to COVID-19 and are at increased risk of progression to hospitalisation or death. The provisional registration was based on short term efficacy and safety data and continued approval is contingent on provision of efficacy and safety data from ongoing clinical trials and post-market assessment. The provisional registration period is 2 years starting on the day registration commences. The Pre-Sub-Committee Response (PSCR) reported that provisional registration has been extended to 18 Jan 2026.

2.2 The submission stated that Pfizer is working to address the post-approval commitments associated with the provisional registration and that, once the data for the commitments currently under evaluation are accepted by the TGA, Pfizer will lodge an application to request conversion to full registration. The submission stated that nirmatrelvir and ritonavir “is not currently expected to have full registration by 1 April 2024”. The PSCR reported that an application to convert the provisional registration to full approval was submitted to the TGA on 30 August 2023.

Previous PBAC considerations

- 2.3 As part of its response to the COVID-19 pandemic, the Australian Government Department of Health and Aged Care, with advice from the COVID-19 Vaccines and Treatments for Australia – Science and Industry Technical Advisory Group (SITAG), made commitments to pre-purchase promising vaccines and therapeutics for COVID-19, subject to TGA registration. One of these was nirmatrelvir and ritonavir, for which a commitment to purchase 500,000 courses for delivery into the National Medical Stockpile (NMS) during 2022 was made.
- 2.4 **January 2022:** The PBAC convened a special meeting on 18 January 2022 to provide preliminary advice to the Minister for Health (Minister) as to whether the drugs, nirmatrelvir and ritonavir (Paxlovid®) and/or molnupiravir (Lagevrio®) and/or tixagevimab with cilgavimab (Evusheld®) could be made available as a pharmaceutical benefit under Part VII of the National Health Act 1953 (Act) for the treatment of SARS-CoV-2 infection in non-hospitalised patients who are at high risk of progression to severe COVID-19 (nirmatrelvir and ritonavir; and molnupiravir) and for Pre-Exposure Prophylaxis (PrEP, Evusheld) in patients at high risk. The PBAC advised the Minister it considered these drugs were suitable for supply to patients through the PBS, subject to approval by the TGA and the requirements of the National Health Act 1953 being met.
- 2.5 Rapid health technology assessments (rapid HTAs) of various treatments for COVID-19, including nirmatrelvir and ritonavir, were commissioned by the Department to inform PBAC decision-making.
- 2.6 Pfizer did not submit an application for the PBS listing of nirmatrelvir and ritonavir. However, Pfizer agreed to the Commonwealth being the Responsible Person for nirmatrelvir and ritonavir for PBS purposes. Pfizer remained the sponsor of nirmatrelvir and ritonavir for the purposes of registration. To enable PBS supply, the Commonwealth committed to purchase an additional 500,000 courses, following advice from the SITAG.
- 2.7 **March 2022:** The PBAC considered the report of the rapid HTA of nirmatrelvir and ritonavir. The primary source of evidence reviewed in the rapid HTA was the EPIC-HR trial. The EPIC-HR trial was conducted in a population of unvaccinated, non-hospitalised adults (aged ≥18 years) with mildly to moderately symptomatic, confirmed COVID-19 (≤ 5 days from onset of symptoms), and at least one risk factor putting them at high risk of progression to severe COVID-19, which may cause hospitalisation or death. The EPIC-SR trial was ongoing at the time of preparation of the rapid HTA. The EPIC-SR trial was conducted in a population of unvaccinated adults with symptomatic COVID-19 who are at ‘standard risk’ of hospitalisation or death as well as vaccinated adults with symptomatic COVID-19 who had one or more risk factors for progressing to severe illness. A number of analysis sets were defined for the EPIC-HR trial. No analyses of outcomes were performed using the full analysis set (FAS). The modified Intent to Treat 2 (mITT2) population was considered the analysis

set that most closely resembled the ITT (FAS) analysis set as it included all patients who received at least one dose of study intervention. The results of the EPIC-HR trial indicated a benefit from treatment with nirmatrelvir and ritonavir, as summarised in Table 2, and indicated that it was generally well tolerated. However, it was noted that the use of nirmatrelvir and ritonavir was contraindicated in a number of patient groups: patients with severe renal impairment, patients with severe hepatic impairments, patients on medications that are highly dependent on cytochrome P4503A (CYP3A) for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions and patients on medications that are potent CYP3A inducers.

Table 2: Hospitalisation or death through Day 28 unadjusted results from the final analysis of outcomes in various populations of patients recruited to the EPIC-HR trial who completed Day 28 assessments (data cutoff 9 December 2021)

Population	PAXLOVID	Placebo	Risk difference (95% CI)	Relative risk (95% CI)	Odds ratio (95% CI)
mITT2	9/1109 (0.8%)	68/1115 (6.1%)	-5.3% (-6.8%, -3.8%)	0.133 (0.067, 0.265)	0.126 (0.063, 0.250)
mITT1 (no mAb)	8/1039 (0.8%)	66/1046 (6.3%)	-5.5% (-7.1%, -4.0%)	0.122 (0.059, 0.252)	0.115 (0.056, 0.238)
mITT (no mAb & ≤3 days from symptom onset)	5/697 (0.7%)	44/682 (6.5%)	-5.7% (-7.7%, -3.8%)	0.111 (0.044, 0.279)	0.105 (0.043, 0.258)

Statistically significant differences are shown in bolded typeface

Populations: mITT2 population = all participants randomly assigned to study intervention, who took at least one dose of study intervention, and with at least one post-baseline visit through Day 28 regardless of treatment with monoclonal antibody [mAb] and regardless of time since symptom onset); mITT population = all participants randomly assigned to study intervention, who took at least one dose of study intervention, with at least one post-baseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody [mAb] treatment and were treated ≤3 days of symptom onset); mITT1 population = all participants randomly assigned to study intervention, who took at least one dose of study intervention, with at least one post-baseline visit through Day 28 visit who, at baseline, did not receive nor were expected to receive COVID-19 therapeutic mAb treatment

Sources: Table 14.2.1.22, Table 13 and Table 11 of the Final Clinical Study Report (data cutoff: 9 December 2021) for the EPIC-HR trial

2.8 An economic analysis was presented in the report of the rapid HTA that indicated that nirmatrelvir and ritonavir was cost-effective when used in a population consistent with the full population recruited to the EPIC-HR trial i.e., unvaccinated patients at high risk of hospitalisation or death. However, sensitivity analyses indicated that the results of the analyses were highly sensitive to the baseline rate of hospitalisation applied in the economic analysis and noted that there was uncertainty in what value was applicable in the Australian setting e.g., vaccinated patients had a lower baseline risk of hospitalisation and the risk of hospitalisation with the Omicron variant was lower than the risk with previous SARS-CoV-2 variants. The PBAC agreed that, based on the available evidence and the health technology assessment, nirmatrelvir and ritonavir treatment was cost-effective for some patients and recommended that nirmatrelvir and ritonavir should be available on the PBS as an Authority Required (STREAMLINED) benefit for the same high-risk patients was eligible for PBS-subsidised molnupiravir.

2.9 The PBAC advised that the cost-effectiveness of nirmatrelvir and ritonavir, should be reviewed but did not specify a timeline for the review.

- 2.10 The listing of nirmatrelvir and ritonavir was implemented on 1 May 2022.
- 2.11 Over time, the PBAC recommended various amendments to the PBS listing of nirmatrelvir and ritonavir. As at 1 February 2023, nirmatrelvir and ritonavir, and also molnupiravir, were PBS-listed for the following high-risk populations:
- (i) people aged ≥ 70 years;
 - (ii) people aged ≥ 18 years who are either moderately to severely immunocompromised with risk of progression to severe COVID-19 disease or have experienced past COVID-19 infection resulting in hospitalisation;
 - (iii) Aboriginal or Torres Strait Islander people aged ≥ 30 years with one or more risk factors (with prior hospitalisation for COVID-19 included as risk factor); and
 - (iv) people aged 50 – 69 years with two or more additional risk factors or a past COVID-19 infection episode resulting in hospitalisation.
- 2.12 **February 2023 & June 2023:** The PBAC recommended amendments of the restriction for nirmatrelvir and ritonavir at its out-of-session meetings in February 2023 and June 2023. In February 2023, the PBAC recommended amendments to permit PBS-reimbursed prescribing of nirmatrelvir and ritonavir for patients aged 60-69 year and one additional risk factor. In June 2023, the PBAC recommended further amendments permitting PBS-reimbursed prescribing of nirmatrelvir and ritonavir in patients aged 50-59 years with one additional risk factor. These amendments of the restriction for nirmatrelvir and ritonavir were intended to apply only on a temporary basis. The PBAC considered that the cost associated with dispensing nirmatrelvir and ritonavir to the expanded population was justified by the benefit of treatment in that population, taking into account that: the costs for each patient course to be supplied under the PBS had already been incurred by the Commonwealth; the proposed approach would potentially reduce the risk of product wastage; and there would be no incremental additional expenditure to the Commonwealth. Given the particular circumstances, the PBAC considered that the amended restrictions would be cost-effective in the expanded populations only “for so long as pharmaceutical benefits dispensed are sourced from the stock already purchased by the Commonwealth, and which might otherwise expire unused.” Consistent with this, the PBAC recommended that the expansions of patient eligibility should only apply until the Commonwealth purchased stock was exhausted or had expired.

3 Requested listing

- 3.1 The Commonwealth currently holds the role of Responsible Person for the supply and distribution of nirmatrelvir and ritonavir through the PBS. The submission requested PBS listing of nirmatrelvir and ritonavir from 1 April 2024, with Pfizer as the Responsible Person.

- 3.2 Table 3 summarises the key elements of the proposed listing of nirmatrelvir and ritonavir. The key difference between the proposed and current listing is in the price per course of nirmatrelvir and ritonavir. The current ex-manufacturer price is \$1,000 per pack. The submission requested a $\%$ increase in the ex-manufacturer price to \$ \mid . The pre-PBAC response offered a revised ex-manufacturer price of \$ \mid per pack (corresponding to a $\%$ increase in the current ex-manufacturer price).
- 3.3 Ordinarily, flow-on price reductions apply for combination items when there is a statutory price reduction of a component drug. A price reduction to single-ingredient ritonavir (Norvir) came into effect on 1 April 2023¹, however the price of Paxlovid was unchanged on that date. The Secretariat noted that a Ministerial discretion under the *National Health Act 1953* in relation to nirmatrelvir and ritonavir was exercised, with the determination giving effect prior to 31 March 2023. The determination is published on the Federal Register of Legislation and can be accessed at www.legislation.gov.au/Details/F2023N00031.
- 3.4 The restrictions proposed for: (i) patients aged 70 or more, (ii) patients who are immunocompromised or have previously experienced a COVID-19 infection resulting in hospitalisation; (iii) patients identifying as Aboriginal or Torres Strait and at high risk; and (iv) patients aged 50 – 69 years at high risk are shown in Table 4, Table 5, Table 6 and Table 7, respectively.
- 3.5 The proposed restrictions are identical to the current restrictions except that, as shown in each of the tables, the submission proposed removal of the ‘Caution’ which is noted in the current restrictions regarding significant drug-drug interactions on the grounds that drug-drug interactions with nirmatrelvir and ritonavir are due to the ritonavir component (which is an inhibitor of CYP3A), with little or no contribution from nirmatrelvir and that the ‘Caution’ is not included in the ritonavir (Norvir®) PBS restriction. It was noted that many commonly used medicines can be safely co-administered with nirmatrelvir and ritonavir and some drug interactions can be safely managed under appropriate clinical supervision. Several tools are available to assist clinicians to identify and manage drug-drug interactions; such as: Liverpool COVID 19 Interactions tool; COVID-19 - National Clinical Evidence Taskforce; Pfizer Australia Medical Information; and NIH COVID-19 Treatment Guidelines.
- 3.6 The DUSC considered the ‘Caution’ could be retained for nirmatrelvir and ritonavir due to the risk of serious adverse reactions due to interactions with other medicines as documented in the TGA-approved Product Information.
- 3.7 The ESC noted that nirmatrelvir and ritonavir is prescribed under Section 85 for the general community. In contrast, ritonavir as a single agent is listed under Section 100 as a highly specialised drug, managed by prescribers who are familiar with the

¹ https://www.pbs.gov.au/info/industry/pricing/catch-up_statutory_price_reductions

medicine and its interactions. The ESC considered that removal of the caution was not advisable given broad use in a general community setting.

- 3.8 The submission sought continued listing of nirmatrelvir and ritonavir as currently applies i.e., including patients aged 50-69 years with only one additional risk factor. However, the pre-PBAC response acknowledged that amendments of the restriction for nirmatrelvir and ritonavir to include access for these patients were intended to apply only on a temporary basis. The possibility that the eligibility criteria for people aged 50-59 and 60-69 years revert to “with at least two additional risk factors” was accounted for in scenario analyses presented in the submission. The pre-PBAC response acknowledged that the cost-effectiveness of Paxlovid in the 50-69 year old subgroup with one additional risk factor is higher than in other patient subgroups as set out the in the ESC advice (see paragraph 6.72). The pre-PBAC response presented analyses based on the following four subgroups only: People aged 70 years old and older, People aged 50-69 years old with at least two additional risk factors, Aboriginal or Torres Strait Islander people aged 30 years and older with at least one additional risk factor and people aged 18 years and older who are moderately or severely immunocompromised.

Table 3: Essential elements of the proposed listing of nirmatrelvir and ritonavir

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NIRMATRELVIR (&) RITONAVIR					
Authority Required (STREAMLINED)					
nirmatrelvir 150 mg tablet [4] (&) ritonavir 100 mg tablet [2], 5 x 6	\$ [submission] \$ [pre-PBAC response]	1	1	0	Paxlovid
Prescriber bag					
nirmatrelvir 150 mg tablet [4] (&) ritonavir 100 mg tablet [2], 5 x 6	\$ [submission] \$ [pre-PBAC response]	2	2	0	Paxlovid

Table 4: Proposed restriction for nirmatrelvir and ritonavir for patients aged ≥ 70 years

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria:
Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
The treatment must be initiated within 5 days of symptom onset; OR The treatment must be initiated as soon as possible after a diagnosis is confirmed where asymptomatic.
Population criteria:
Patient must be at least 70 years of age.
Prescribing Instructions:

<p>Access to this drug through this restriction is permitted irrespective of vaccination status.</p> <p>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.</p> <p>Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.</p> <p>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.</p> <p>Caution: Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Paxlovid Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.</p>

Table 5: Proposed restriction for nirmatrelvir and ritonavir for patients who are immunocompromised or have previously experienced a COVID-19 infection resulting in hospitalisation

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria:
Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must have at least one sign or symptom attributable to COVID-19
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
Patient must satisfy at least one of the following criteria: (i) be moderately to severely immunocompromised with risk of progression to severe COVID-19 disease due to the immunocompromised status, (ii) has experienced past COVID-19 infection resulting in hospitalisation,
AND
The treatment must be initiated within 5 days of symptom onset
AND
Patient must be at least 18 years of age.
Prescribing Instructions:
For the purpose of administering this restriction, 'moderately to severely immunocompromised' patients are those with:
1. Any primary or acquired immunodeficiency including:
a. Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders,
b. Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),
c. Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency; OR
2. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received:
a. Chemotherapy or whole body radiotherapy,
b. High-dose corticosteroids (at least 20 mg of prednisone per day, or equivalent) for at least 14 days in a month, or pulse corticosteroid therapy,
c. Biological agents and other treatments that deplete or inhibit B cell or T cell function (abatacept, anti-CD20 antibodies, BTK inhibitors, JAK inhibitors, sphingosine 1-phosphate receptor modulators, anti-CD52 antibodies, anti-complement antibodies, anti-thymocyte globulin),

<p>d. Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) including mycophenolate, methotrexate, leflunomide, azathioprine, 6-mercaptopurine (at least 1.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus); OR</p> <p>3. Any significantly immunocompromising condition(s) where, in the last 12 months the patient has received an anti-CD20 monoclonal antibody treatment, but criterion 2c above is not met; OR</p> <p>4. Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies; OR</p> <p>5. People with disability with multiple comorbidities and/or frailty.</p> <p>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.</p> <p>For the purpose of administering this restriction, signs or symptoms attributable to COVID-19 are: fever greater than 38 degrees Celsius, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell.</p> <p>Access to this drug through this restriction is permitted irrespective of vaccination status.</p> <p>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.</p> <p>Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.</p> <p>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.</p> <p>Caution: Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Paxlovid Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.</p>
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Table 6: Proposed restriction for nirmatrelvir and ritonavir for Aboriginal and Torres Strait Islander people

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria:
Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must have at least one sign or symptom attributable to COVID-19
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
The treatment must be initiated within 5 days of symptom onset
Population criteria:
Patient must be each of: (i) identify as Aboriginal or Torres Strait Islander, (ii) at least 30 years of age, (iii) at high risk.
Prescribing Instructions:
For the purpose of administering this restriction, high risk is defined as the presence of at least one of the following conditions:
1. The patient is in residential aged care
2. The patient has disability with multiple comorbidities and/or frailty
3. Neurological conditions, including stroke and dementia and demyelinating conditions

<p>4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease</p> <p>5. Heart failure, coronary artery disease, cardiomyopathies</p> <p>6. Obesity (BMI greater than 30 kg/m²)</p> <p>7. Diabetes type I or II, requiring medication for glycaemic control</p> <p>8. Renal impairment (eGFR less than 60mL/min)</p> <p>9. Cirrhosis</p> <p>10. The patient has reduced, or lack of, access to higher level healthcare and lives in an area of geographic remoteness classified by the Modified Monash Model as Category 5 or above</p> <p>11. Past COVID-19 infection episode resulting in hospitalisation.</p> <p>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.</p> <p>For the purpose of administering this restriction, signs or symptoms attributable to COVID-19 are: fever greater than 38 degrees Celsius, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell.</p> <p>Access to this drug through this restriction is permitted irrespective of vaccination status.</p> <p>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.</p> <p>Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.</p> <p>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.</p> <p>Administrative Advice: The Modified Monash Model categorises an area according to geographical remoteness and town size. Details can be found at: https://www.health.gov.au/health-topics/rural-health-workforce/classifications/mmm</p> <p>Caution: Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Paxlovid Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.</p>
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Table 7: Proposed restriction for nirmatrelvir and ritonavir for patients aged 50 - 69 years with one additional risk factor

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria: Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must have at least one sign or symptom attributable to COVID-19
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
The treatment must be initiated within 5 days of symptom onset
Population criteria:
Patient must be at high risk of requiring hospitalisation for COVID-19 infection
AND
Patient must be at least 50 years old, but not older than 60 years; or

<p>Patient must be at least 60 years old, but not older than 70 years</p>
<p>Prescribing Instructions: For the purpose of administering this restriction, high risk is defined as the presence of at least one of the following conditions:</p> <ol style="list-style-type: none">1. The patient is in residential aged care2. The patient has disability with multiple comorbidities and/or frailty3. Neurological conditions, including stroke and dementia and demyelinating conditions4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease5. Heart failure, coronary artery disease, cardiomyopathies6. Obesity (BMI greater than 30 kg/m²)7. Diabetes type I or II, requiring medication for glycaemic control8. Renal impairment (eGFR less than 60mL/min)9. Cirrhosis10. The patient has reduced, or lack of, access to higher level healthcare and lives in an area of geographic remoteness classified by the Modified Monash Model as Category 5 or above11. Past COVID-19 infection episode resulting in hospitalisation. <p>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.</p> <p>For the purpose of administering this restriction, signs or symptoms attributable to COVID-19 are: fever greater than 38 degrees Celsius, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell.</p> <p>Access to this drug through this restriction is permitted irrespective of vaccination status.</p> <p>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.</p> <p>Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.</p> <p>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.</p>
<p>Caution: Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Paxlovid Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.</p>

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. SARS-CoV-2 is a positive-sense single stranded (+ss) RNA virus. It belongs to the genus β -coronavirus of the family Coronaviridae. Most patients who fall sick with COVID-19 experience mild to moderate symptoms such as fever, cough, tiredness and loss of smell, and recover without clinical or therapeutic intervention. However, some patients can become seriously ill and require hospitalisation as a consequence of respiratory complications, aberrant immune response resulting in hyperinflammation or decompensation of underlying health conditions. Of patients who are admitted to hospital with COVID-19, a proportion require admission to an intensive care unit (ICU)

and, in some cases, require mechanical ventilation. Some patients die either directly or indirectly due to COVID-19.

- 4.2 Nirmatrelvir is an inhibitor of SARS-CoV-2 main protease (M^{pro}). Inhibition of M^{pro} leads to the prevention of viral replication. Nirmatrelvir is co-administered with ritonavir. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
- 4.3 Nirmatrelvir and ritonavir should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset in adults who are at risk for progression to severe COVID-19, which may necessitate hospitalisation.
- 4.4 The recommended dosage is 300 mg nirmatrelvir (administered as two 150 mg tablets) with 100 mg ritonavir (administered as a single 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. For patients with moderate renal impairment, a reduced dose of 150 mg nirmatrelvir (administered as one 150 mg tablets) with 100 mg ritonavir (administered as a single 100 mg tablet) is recommended to be taken twice daily for 5 days. Nirmatrelvir and ritonavir is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73m²).
- 4.5 The TGA-approved product information states that potential drug-drug interactions should be considered prior to treatment with nirmatrelvir and ritonavir and adverse reactions associated with concomitant medications monitored during treatment. The submission reported that 5%-10% of people are contraindicated to nirmatrelvir and ritonavir due to drug-drug interactions based on a study of US patient electronic health records in the 12 months ending September 2022 (Pfizer, data on file²). It was reported that approximately 10% of high-risk patients aged 18 and over would be contraindicated for nirmatrelvir and ritonavir based on their prescription patterns, and if adjusting for contraindicated medicines that could be safely paused or are given in inpatient settings (and therefore not relevant to the outpatient context), approximately 5% would have a contraindication. The submission also cited two publications that reported approximately 15% of patients had a possible contraindication (Lim 2022³ and Hoertel 2022⁴). Hoertel (2022) reported that 15% of the study cohort of hospitalised patients in Paris, France, had a medical contraindication to nirmatrelvir and ritonavir with higher rates in older patients (27%) than younger patients (9%), and in those with comorbidities (>37% for most comorbidities) than without comorbidities (4%). The ESC considered the applicability of these data to the Australian setting was uncertain. One of the tools widely used to determine whether a drug-drug interaction with nirmatrelvir and ritonavir is possible is the Liverpool drug interaction checker. Although some of the interactions can be

2 Pfizer. Internal data on file (Based on Optum US EHR Data) 28 June 2023.

3 Lim S, Tignanelli CJ, Hoertel N, Boulware DR, Usher MG. Prevalence of Medical Contraindications to Nirmatrelvir/Ritonavir in a Cohort of Hospitalized and Nonhospitalized Patients With COVID-19. *Open Forum Infect Dis.* 2022 Aug 3;9(8):ofac389. doi: 10.1093/ofid/ofac389.

4 Hoertel N, Boulware DR, Sánchez-Rico M, Burgun A, Limosin F. Prevalence of Contraindications to Nirmatrelvir-Ritonavir Among Hospitalized Patients With COVID-19 at Risk for Progression to Severe Disease. *JAMA Netw Open.* 2022 Nov 1;5(11):e2242140.

avoided by dose reduction or withholding treatment, there are multiple factors that may preclude a clinician from adopting such approaches e.g., patients may have cognitive issues; patients may become anxious if advised to discontinue a medication temporarily; patients may have comorbidities that present challenges e.g., severe renal or hepatic impairment; clinicians may have concerns about the safety of withdrawing a therapy e.g., if a patient is taking carbamazepine or amiodarone or apixaban. Quantifying the proportion of patients in whom nirmatrelvir and ritonavir is appropriate is difficult. Although an assumption that it can be used in 10% of patients may be an overestimate, the current market share of nirmatrelvir and ritonavir of approximately 10% is likely to be an underestimate of the achievable proportion.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission, appropriately, nominated placebo (representative of usual care with no SARS-CoV-2 antiviral medication) as the main comparator and molnupiravir as a relevant secondary comparator.
- 5.2 As noted in the submission, an Administrative Note was added to the restriction for molnupiravir on 1 January 2023 indicating that it should be considered for use only if nirmatrelvir (& ritonavir is contraindicated or otherwise unsuitable. The PBAC considered a submission for molnupiravir at the July 2023 meeting and advised that additional information was required to inform further consideration of molnupiravir⁵.
- 5.3 The submission claimed that prevalence of contraindications to nirmatrelvir and ritonavir is relatively low. It suggested that the share of the COVID-19 treatment market held by molnupiravir, approximately 59%, suggested that molnupiravir was not being prescribed in accordance with the Note added to the PBS restriction on 1 January 2023. The submission did not differentiate between patients with an absolute versus relative contraindication to ritonavir. Although it may be theoretically possible to avoid a potential drug-drug interaction (DDI) with ritonavir, there is potential for a high proportion of patients to be at risk of a DDI with ritonavir (and therefore nirmatrelvir and ritonavir) based on their regular medication.
- 5.4 The PSCR reiterated the submission's claim that only 5% of patients have an absolute contraindication. The ESC was of the view that considering absolute contraindications only oversimplified the potential challenges of real world prescribing, and while it is appropriate to assume doctors are familiar and capable of managing the complexities of drug interactions, the choice of which antiviral to prescribe when a high-risk patient is diagnosed with COVID-19 is multifaceted and extends beyond whether a potential drug-drug interaction can be avoided by withholding a treatment.

⁵ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2023-07/pbac-web-outcomes-07-2023-v2.pdf>

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3), and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nirmatrelvir and ritonavir including potential to reduce symptoms and prevent severe COVID. The input also described concerns about long COVID, and a desire for expanded access to the medicine beyond the groups that are eligible currently. The input also described concerns about the cost of treatment for those not eligible for PBS access.
- 6.3 The Lung Foundation Australia (LFA) described the health, financial and social cost of COVID-19 in Australia. The input supported the ongoing PBS listing of nirmatrelvir and ritonavir for people at increased risk of severe disease, noting that benefits may include reduced risk of severe infection, hospitalisation, and death in people with mild to moderate COVID-19. Additional benefits may include reduced duration of the person feeling unwell. It was also stated that nirmatrelvir and ritonavir was more efficacious than other treatments and could reduce burden on the healthcare system.
- 6.4 The input from Rare Cancers Australia (RCA) discussed that people living with cancer have increased vulnerability to SARS-CoV-2 infection and development of more severe COVID-19 symptoms. The input noted that people living with cancer may be immunocompromised and supported ongoing PBS access for this patient group. The input highlighted the importance of commencing treatment without delay. For people living with cancer, additional benefits are to reduce acute symptoms and minimise disruption to cancer treatment. The input also supported the recommendations from the Long COVID Senate Inquiry for access to OAVs to be expanded⁶.
- 6.5 The PBAC noted that this input was largely supportive of the evidence provided in the submission, however the evidence presented in the submission regarding the impact of treatment with nirmatrelvir and ritonavir on long COVID was inconclusive (see paragraphs 6.37 to 6.41).

Clinical trials and observational studies

- 6.6 The submission presented two randomised, double-blind, placebo-controlled trials of nirmatrelvir and ritonavir (EPIC-HR and EPIC-SR).

⁶ <https://www.aph.gov.au/longandrepeatedcovid>

- The EPIC-HR trial was the primary source of evidence considered by the PBAC when it recommended listing of nirmatrelvir and ritonavir on the PBS in March 2022. The trial was conducted in unvaccinated patients diagnosed with COVID-19 who were at high risk of developing severe COVID-19, which can necessitate hospitalisation.
- The second randomised, double-blind, placebo-controlled trial (EPIC-SR) was ongoing at the time of the PBAC consideration of nirmatrelvir and ritonavir in March 2022 but has since reported. The submission provided limited details for the ITT population recruited to this trial on the grounds that the majority of patients in the trial fall outside of the TGA-approved indication for nirmatrelvir and would not be eligible for treatment with nirmatrelvir and ritonavir on the PBS due to being at 'standard risk' of developing severe COVID-19. However, the submission presented analyses of outcomes in a subgroup of patients recruited to the EPIC-SR trial who were vaccinated, had been diagnosed with COVID-19 and were considered by the submission to be at high risk of developing severe COVID-19. High risk was defined as having at least one risk factor. Risk factors included age ≥ 60 (65 for 2022 enrolees⁷), body mass index (BMI) > 25 (≥ 30 for 2022 enrolees), and with any of the following recorded in the medical history: cigarette smoker, chronic kidney disease, hypertension, diabetes mellitus, cardiovascular disorder, chronic lung disease, HIV infection, sickle cell disease, neurodevelopmental disorder, cancer and device dependence).

6.7 No head-to-head trials comparing nirmatrelvir and ritonavir to molnupiravir were located. However, the submission located and presented two randomised placebo-controlled trials of molnupiravir.

- The MOVE-out trial was the primary source of evidence considered by the PBAC when it recommended listing of molnupiravir on the PBS in February 2022. The trial was conducted in unvaccinated patients with COVID-19 who were at high risk of developing severe COVID-19.
- The other trial (PANORAMIC) was a randomised, open-label, placebo-controlled trial conducted in vaccinated, adult patients with COVID-19 at increased risk of adverse outcomes. The PBAC considered this trial at its meeting in November 2022 and noted that participants in this trial were, as a whole, younger than patients receiving molnupiravir in Australia ($< 15\%$ of patients in the trial were ≥ 70 years whereas approximately two-thirds of PBS utilisation of molnupiravir had been in patients aged ≥ 70 years) and noted that patients at highest risk of progression to severe disease were not the target population recruited to PANORAMIC.

⁷ Risk factors for age and BMI were conditional based on when participants enrolled. The protocol was amended on 21 January 2022 to change age risk factor from ≥ 60 years to ≥ 65 years and change BMI risk factor from ≥ 25 kg/m² to ≥ 30 kg/m².

- 6.8 As noted by the submission, a nirmatrelvir and ritonavir arm was added to the PANORAMIC trial. However, results for nirmatrelvir and ritonavir in the PANORAMIC trial had not, to date (August 2023), been reported.
- 6.9 In addition to the randomised trials, the submission presented information from nine observational studies comparing outcomes in patients treated with nirmatrelvir and ritonavir to untreated patients. Over 20 potentially relevant observational studies were located during the evaluation and many of these were included in the two published meta-analyses discussed in paragraphs 6.11 and 6.29. The majority of these studies were identified by the literature search presented in the submission but were excluded for various reasons.
- 6.10 Three observational studies comparing outcomes in molnupiravir-treated patients to untreated patients were also presented in the submission. As with the studies for nirmatrelvir and ritonavir, some additional potentially relevant observational studies of molnupiravir were located during the evaluation.
- 6.11 The submission did not present any meta-analyses based on the trials and studies presented in the submission. However, the submission did present results from two published meta-analyses (Amani 2023 and Cheema 2023). These published meta-analyses did not include all of the studies located by the submission's search of the literature. Furthermore, the meta-analyses, included 20 observational studies beyond those presented and assessed in the submission. Some of these studies did not meet the inclusion criteria that were specified for consideration in the submission e.g., due to sample size being < 1000, due to vaccination rates being low, study conducted in a special population.
- 6.12 Due to the meta-analyses being incomplete (i.e., the meta-analyses excluded some of the observational studies that were identified as relevant by the submission [Kaboré 2023, Lewnard 2023, Najjar-Debbiny 2023a]) and due to inconsistent application of inclusion/exclusion criteria to the studies for presentation in the submission versus the ones applied for inclusion/exclusion in the meta-analyses (i.e., the submission excluded many of the studies included by the meta-analyses e.g., due to size of the cohorts), there was not a consolidated presentation of observational studies in the submission.
- 6.13 The submission presented two published meta-analyses of molnupiravir vs placebo (Benaicha 2023 and Huang 2023). As with the meta-analyses presented for nirmatrelvir and ritonavir, the meta-analyses excluded studies deemed relevant by the submission (Yip 2019) and included studies beyond those identified as being relevant by the submission. The meta-analysis reported by Benaicha 2023 was used to inform the economic analysis comparing molnupiravir to placebo.
- 6.14 The submission did not present any indirect comparisons of molnupiravir versus nirmatrelvir and ritonavir. Although this may be reasonable if there was potential for a lack of exchangeability of patients in the trials, an indirect comparison should have been presented given an economic evaluation comparing nirmatrelvir and ritonavir to

molnupiravir was presented in the economics section of the submission, which was based on the results of published meta-analyses.

- 6.15 Details of the trials and observational studies presented in the submission are provided in Table 8.
- 6.16 One of the additional studies located during the evaluation (van Heer 2023⁸) would have met the submission’s exclusion criteria on the basis that the manuscript had not undergone peer review, but has been added to the list of observational studies in Table 8. Results are presented for this study as it was conducted in Victoria, Australia and is potentially relevant, particularly for the 70+ subgroup, as it reflected outcomes in a population aged ≥ 70 years who met the PBS criteria for access to antivirals and were treated in the Australian healthcare system. Although the analyses reported by van Heer 2023 were adjusted to address potential confounding due to differences in age, sex, socioeconomic status, history of hospitalisation, aged care resident status and vaccination status, the study is subject to bias and confounding associated with observational studies.

Table 8: Trials and observational studies and associated reports presented in the submission and identified during the evaluation

Study ID	Protocol title/ Publication title	Publication citation
Randomised controlled trials of nirmatrelvir and ritonavir		
EPIC-HR	Final clinical study report (CSR). An interventional, efficacy and safety, phase 2/3, double-blind, 2-arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progressing to severe illness Hammond et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19.	9 March 2023 NEJM. 2022;386(15):1397-1408
EPIC-SR	CSR. An Interventional efficacy and safety, phase 2/3, double-blind, 2 arm study to investigate orally administered PF-07321332/Ritonavir compared with placebo in non-hospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness.	10 March 2023
Randomised controlled trials of molnupiravir		
MOVE-OUT	Bernal et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients.	NEJM. 2022;386(6):509-520
	Johnson et al. Effect of Molnupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19: A Randomised, Placebo-Controlled Trial.	Ann Intern Med. 2022;175(8):1126-1134
	Johnson et al. Molnupiravir for the treatment of COVID-19 in immunocompromised participants: efficacy, safety, and virology results from the phase 3 randomised, placebo-controlled MOVE-OUT trial.	Infection. 2023 [Epub ahead of print]

⁸ Van Heer, Christina, et al. "Effectiveness of community-based oral antiviral treatments against severe COVID-19 outcomes in people 70 years and over in Victoria, Australia, 2022: an observational study." *The Lancet Regional Health–Western Pacific* 41 (2023). <http://dx.doi.org/10.2139/ssrn.4495142>; subsequently published at <https://doi.org/10.1016/j.lanwpc.2023.100917>

Study ID	Protocol title/ Publication title	Publication citation
PANORAMIC	Butler et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial.	Lancet. 2023;401(10373):281-293
Observational cohort studies of nirmatrelvir and ritonavir only		
Aggarwal 2023	Aggarwal NR et al. Real-world use of nirmatrelvir-ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study.	Lancet Infect Dis. 2023;23(6):696-705
Arbel 2022*	Arbel R, et al. Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge.	NEJM. 2022; 387(9):790-798
Dryden-Peterson 2023	Dryden-Peterson et al. Nirmatrelvir Plus Ritonavir for Early COVID-19 in a Large U.S. Health System: A Population-Based Cohort Study.	Ann Intern Med. 2023;176(1):77-84
Ganatra 2023	Ganatra et al. Oral Nirmatrelvir/ritonavir in Nonhospitalized Vaccinated Patients With Coronavirus Disease 2019.	Clin Infect Dis. 2023;76(4):563-572
Kaboré 2023	Kaboré JL et al 2023. Real-World Effectiveness of Nirmatrelvir/Ritonavir on Covid-19-Associated Hospitalisation Prevention: A Population-Based Cohort Study in the Province of Québec, Canada.	Clin Infect Dis. 2023;ciad287
Lewnard 2023	Lewnard JA et al. Effectiveness of nirmatrelvir-ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system.	Lancet Infect Dis. 2023:S1473-3099(23)00118-4
Observational cohort studies of nirmatrelvir and ritonavir and molnupiravir		
Najjar-Debbiny 2023a	Najjar-Debbiny R et al. Effectiveness of Paxlovid in Reducing Severe Coronavirus Disease 2019 and Mortality in High-Risk Patients.	Clin Infect Dis. 2023;76(3):E342-E349
Najjar-Debbiny 2023b	Najjar-Debbiny R et al. Effectiveness of Molnupiravir in High-Risk Patients: A Propensity Score Matched Analysis.	Clin Infect Dis. 2023;76(3):453-460.
Wong 2022	Wong CKH et al. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study.	Lancet. 2022;400(10359):1213-1222.
Yip 2023	Yip TC et al. Impact of the Use of Oral Antiviral Agents on the Risk of Hospitalisation in Community Coronavirus Disease 2019 Patients (COVID-19).	Clin Infect Dis. 2023;76(3):e26-e33.

* a preprint of a matching study for molnupiravir was located during the evaluation: <https://www.researchsquare.com/article/rs-2115769/v1>
Abbreviations: Ann Intern Med = Annals of Internal Medicine; ciad = Clinical Infectious Diseases Advance Access; Clin Infect Dis. = Clinical Infectious Diseases; J Infect = Journal of Infection; Lancet Infect Dis.= The Lancet Infectious Diseases; NEJM = New England Journal of Medicine

Source: Tables 2.2.3 and 2.2.4 on pp 39-42 of the submission

6.17 Details of the meta-analyses presented in the submission are provided in Table 9.

Table 9: Meta-analyses presented in the submission

Study ID	Publication title	Publication citation
Primary comparator: nirmatrelvir and ritonavir vs placebo		
Cheema 2023	Cheema H.A. et al. 2023. Nirmatrelvir-ritonavir for the treatment of COVID-19 patients: A systematic review and meta-analysis.	Journal of Medical Virology. 95(2) (no pagination), 2023. Article Number: e28471. Date of Publication: February 2023.
Amani 2023	Amani B, Amani B. Efficacy and safety of nirmatrelvir/ritonavir (Paxlovid) for COVID-19: A rapid review and meta-analysis.	J Med Virol. 2023 Feb;95(2):e28441

Study ID	Publication title	Publication citation
Secondary comparator: molnupiravir vs placebo		
Huang 2023	Huang, C et al. 2023 Real-World Clinical Outcomes of Molnupiravir for the Treatment of Mild to Moderate COVID-19 in Adult Patients during the Dominance of the Omicron Variant: A Meta-Analysis.	Antibiotics 2023, 12, 393.
Benaicha 2023	Benaicha K, Khenhrani RR, Veer M, Devi S, Shahbaz U, Salah QM, Hammad M, Palleti SK. Efficacy of Molnupiravir for the Treatment of Mild or Moderate COVID-19 in Adults: A Meta-Analysis.	Cureus. 2023 May 5;15(5):e38586.

- 6.18 The usual preference of PBAC is for effectiveness to be based on randomised clinical trials. The key features of the randomised trials considered by the submission are summarised in Table 10.
- 6.19 The RCTs were assessed as being associated with a low risk of bias. Although the PANORAMIC trial was an open-label trial, the key outcomes of interest to the submission (i.e., rates of hospitalisation and death) are relatively objective outcomes.
- 6.20 All of the observational studies were assessed as being inherently associated with a substantial risk of bias given that all of the studies were retrospective cohort studies and were thus subject to confounding due to potential for differences across treatment groups in unreported or unmeasured patient characteristics.
- 6.21 Applicability issues are relevant for all of the trials presented in Table 10. In particular, the variation in the study periods examined by the trials could mean that the evidence would not be applicable to the current scenario (in terms of variants circulating, in terms of proportion of the population vaccinated, etc) and variations in the settings in which the studies were conducted could mean that the data would not be applicable to the Australian setting (e.g., if routine care before and after hospitalisation in the studies was different to that experienced by patients in Australia, if the thresholds for referring patients for admission to hospital were different to those applying in Australia).
- 6.22 Patients in each of the trials and studies were prescribed the recommended doses and course of treatment with either nirmatrelvir and ritonavir or molnupiravir.

Table 10: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
Nirmatrelvir and ritonavir versus placebo RCTs					
EPIC-HR	2,246	R, DB, MC 24 weeks Jul-Dec 2021	Low	Non-hospitalised, unvaccinated adults with mild or moderate COVID-19 and ≥1 risk factor diagnosed within 5 days of symptom onset	All cause hospitalisation or death
EPIC-SR	1,440	R, DB, MC 24 weeks Aug 2021-Jul 2022	Low	Non-hospitalised, unvaccinated adults with ≥ 1 symptom & within 5 days of symptom onset of COVID-19 who have a standard risk profile for progression to severe illness	Time to alleviation of symptoms, all cause hospitalisation or death

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Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
Nirmatrelvir and ritonavir versus placebo RCTs					
Molnupiravir versus placebo RCTs					
MOVE-OUT	1,433	R, DB, MC 4 weeks follow-up May-Nov 2021	Low	Non-hospitalised, unvaccinated adults with mild or moderate COVID-19 and ≥ 1 risk factor diagnosed within 5 days of symptom onset	All cause hospitalisation or death
PANORAMIC	25,708	R, OL, MC 4 weeks follow-up Dec 2021 – Apr 2022	Low	Vaccinated and unvaccinated non-hospitalised adults with COVID-19 aged ≥ 50 years (or ≥ 18 years with relevant comorbidities) diagnosed within 5 days of symptom onset	All cause hospitalisation or death
Observational studies comparing patients treated with nirmatrelvir and ritonavir, patients treated with molnupiravir and untreated patients contemporaneously					
Arbel 2022*	109,254	Retrospective cohort 35 days follow-up Jan-Mar 2022	Observational	Vaccinated and unvaccinated, non-hospitalised adults aged ≥ 40 years with confirmed SARS-CoV-2 infection at high risk for progression to severe COVID	Hospitalisation due to COVID-19 or death due to COVID-19
Najjar-Debbiny 2023a	180,351	Retrospective cohort 4 weeks follow-up Jan-Feb 2022	Observational	Vaccinated and unvaccinated, non-hospitalised adults aged ≥ 18 years with ≥ 1 comorbidities or condition associated with high risk of progression to severe COVID	Severe COVID-19 or COVID-19-related death
Najjar-Debbiny 2023b	5,322	Retrospective cohort 4 weeks follow-up Jan-Feb 2022	Observational	Vaccinated and unvaccinated, non-hospitalised adults aged ≥ 18 years with ≥ 1 comorbidities or condition associated with high risk of progression to severe COVID	Severe COVID-19 or COVID-19-related death
Van Heer 2023	38,933	Retrospective cohort 35 days follow-up Jul-Oct 2022	Observational	Vaccinated, non-hospitalised adults aged ≥ 70 years who were diagnosed with COVID-19 and reported to the Victorian Department of Health	All cause hospitalisation or death
Wong 2022	60,214 ^a 54,217 ^b	Retrospective cohort 4 weeks follow-up Feb-Jun 2022	Observational	Vaccinated and unvaccinated, non-hospitalised adults aged ≥ 18 years admitted within 5 days of symptom onset in an outpatient setting	All cause hospitalisation or death
Yip 2023	9,679 ^a 9,556 ^b	Retrospective cohort 30 days follow-up Feb-Mar 2022	Observational	Vaccinated and unvaccinated, non-hospitalised patients admitted within 5 days of symptom onset in an outpatient setting	All cause hospitalisation or death
Observational studies comparing outcomes in patients treated with nirmatrelvir and ritonavir and untreated patients contemporaneously					
Aggarwal 2023	16,529	Retrospective cohort 28 days follow-up Mar-Aug 2022	Observational	Vaccinated and unvaccinated, non-hospitalised adults infected with SARS-CoV-2	All cause hospitalisation or death
Dryden-Peterson 2023	44,551	Retrospective cohort Jan-Jul 2022	Observational	Vaccinated and unvaccinated, non-hospitalised adults aged ≥ 50 years with no contraindications for nirmatrelvir and ritonavir	Hospitalisation within 14 days or death within 28 days

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
Nirmatrelvir and ritonavir versus placebo RCTs					
Ganatra 2023	2,260	Retrospective cohort 30 day follow-up Dec 2021 – Apr 2022	Observational	Vaccinated, non-hospitalised adults aged ≥18 years	All cause ER visit, hospitalisation or death
Kaboré 2023	16,804	Retrospective cohort 30 days follow-up Mar-Oct 2022	Observational	Vaccinated and unvaccinated, non- hospitalised patients	COVID-19 related hospitalisation
Lewnard 2023	133,426	Retrospective cohort 30 days follow-up Apr-Oct 2022	Observational	Vaccinated and unvaccinated, non- hospitalised patients aged ≥12 years	All cause hospitalisation or death

* a preprint of a matching study for molnupiravir was located during the evaluation: <https://www.researchsquare.com/article/rs-2115769/v1>

^a for comparison of nirmatrelvir and ritonavir vs usual care

^b for comparison of molnupiravir vs usual care

Sources: Sections 2.3 and 2.4 on pp43-63, Table 2.3.1 on p44, Table 2.3.2 on pp,46-47, Section 2.4.1 on p55-57, Section 2.6.2 on pp132-137 of the submission, Table 6 of the EPIC-SR CSR, Section 1.1 on pp1-4 and Section 1.3 on pp9-11 of Attachment 3 to the submission

Abbreviations: Aug = August; DB = double blind; Dec = December Jul = July; MC = multi-centre; N = number randomised;

Nov = November; OL = open label; R = randomised.

Comparative effectiveness

6.23 Table 11 summarises the results from each of the trials for the key outcome of proportion of patients hospitalised or died (due to any cause) through Day 28 from each of the trials. There is significant variation in the estimates of treatment effect of nirmatrelvir and ritonavir reported by the various studies. The PSCR stated that variation in estimates of treatment effect was expected, due to differing populations (and high-risk subgroups), vaccine histories, countries and variants. The PSCR noted that the evidence presented in the submission included the EPIC-HR randomised controlled trial conducted at the time of the Delta variant in an unvaccinated population, and more recent observational studies conducted in a highly vaccinated and boosted population with predominance of the Omicron variant.

EPIC-HR

6.24 As noted in paragraph 2.7, a number of analysis sets were defined for the EPIC-HR trial. No analyses of outcomes were performed using the full analysis set (FAS), which included 2,113 patients. The definitions of the other key analysis sets upon which effectiveness of nirmatrelvir and ritonavir was assessed were:

- modified intention-to-treat (mITT) analysis set (N=1,318): all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset;
- mITT1 analysis set (N=1,966): all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment;

- mITT2 analysis set (N=2,091): all participants randomly assigned to study intervention, who took at least 1 dose of study intervention.

The submission focussed on results reported for the mITT analysis set, which was limited to patients who were treated ≤ 3 days of COVID-19 onset. The submission's focus on results based on this subgroup of patients in the trial was not justified given that the population for whom continued availability of nirmatrelvir and ritonavir is sought permits patients to be treated within ≤ 5 days of onset of COVID-19 rather than ≤ 3 days. As discussed in paragraph 2.10, the PBAC considered analyses based on the mITT2 population to be the most relevant analysis set as it included all patients who received at least one dose of study intervention. The mITT2 analysis set is also consistent with the safety analysis set. Thus, results presented in Table 11 are not those reported in the submission but are the results reported for the mITT2 population.

EPIC-SR

- 6.25 The EPIC-SR trial was terminated early. The submission reports that early termination was “due to a very low rate of hospitalisation or death observed in the standard-risk patient population”. Results are presented based on the mITT1 analysis set, which included all participants randomly assigned to study intervention, who took at least 1 dose of study intervention. As can be seen from Table 11, the difference in the EPIC-SR trial in the proportion of patient who had been hospitalised or had died through to Day 28 did not reach statistical significance. In addition, the primary analysis result (difference in time to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28) was not statistically significant and the primary objective of the trial was not met. As shown in Table 11, the submission also presented results from prespecified subgroup analyses that restricted analysis to patients who were considered at high risk (defined as having at least one risk factor). The difference between nirmatrelvir and ritonavir versus placebo again did not reach statistical significance. However, on the EPIC-SR trial, the submission concluded that “the risk reduction was more apparent in the subgroup of participants who were considered as high risk (i.e., vaccinated with at least 1 risk factor) than in participants who were considered as standard risk (i.e., participants who did not have risk factors and were either vaccinated or not vaccinated)”. Overall, the ESC considered that a claim of superiority was supported for high risk patients, including vaccinated patients however, the data were less convincing for patients at lower risk of developing severe COVID 19. The ESC noted that estimates of treatment effect (in terms of incidence of hospitalisation or death) from EPIC-SR (including the high risk subgroup) and some of the observational studies did not reach statistical significance. The ESC considered that, overall, the treatment effect of nirmatrelvir and ritonavir in practice appeared to be less than what was expected at the time it was recommended for inclusion on the PBS based on the results of EPIC-HR.

Table 11: Key results from the studies presented in the submission

Study (and subgroup)	Endpoint	Nirmatrelvir and ritonavir n/N (%)	Placebo n/N (%)	Molnupiravir n/N (%)	RR nirmatrelvir and ritonavir vs placebo (95% CI)	RR molnupiravir vs placebo (95% CI)
RANDOMISED TRIALS						
EPIC-HR	Hospitalisation or death	10/1038 (1.0%)	66/1053 (6.3%)	n/a	0.15 (0.08, 0.30)	n/a
EPIC-SR (mITT1)	Hospitalisation or death	5/654 (0.76%)	10/634 (1.58%)	n/a	0.48 (0.17, 1.41)	n/a
EPIC-SR (subgroup*)	Hospitalisation or death	3/317 (0.95%)	7/214 (2.23%)	n/a	0.29 (0.08, 1.11)	
MOVE-OUT	Hospitalisation or death	n/a	68/699 (9.7%)	48/709 (6.8%)		0.70 (0.49, 0.99)
PANORAMIC	Hospitalisation or death	n/a	98/12525 (0.78%)	105/12529 (0.84%)	n/a	1.07 (0.81, 1.41)
OBSERVATIONAL STUDIES						
Arbel 2022 ≥65 years	Hospitalisation due to COVID-19	11/2,484 (0.44%)	766/40,337 (1.9%)	n/a	0.27[^] (0.15, 0.49)	n/a
	Death due to COVID-19	2/2,484 (0.08%)	158/40,337 (3.9%)	n/a	0.21[^] (0.05, 0.82)	n/a
Arbel 2022 40-64 years	Hospitalisation due to COVID-19	7/1,418 (4.9%)	327/65,015 (0.5%)	n/a	0.74 [^] (0.35, 1.58)	n/a
	Death due to COVID-19	1/1,418 (0.07%)	16/65,015 (0.02%)	n/a	1.32 [^] (0.16, 10.75)	n/a
Najjar-Debbiny 2023a	Death or severe COVID-19	39/4,737 (0.8%)	903/175,614 (0.5%)	n/a	0.54[^] (0.39, 0.75)	n/a
Najjar-Debbiny 2023b	Death or severe COVID-19	n/a	60/2661 (2.25%)	50/2661 (1.88%)	n/a	0.83 (0.57, 1.21)
Wong 2022	Hospitalisation	239/5,542 (4.31%)	3,107/54,672 (5.68%)	n/a	0.76 (0.67, 0.86)	n/a
	Death	9/5,542 (0.17%)	383/54,672 (0.70%)	n/a	0.23 (0.12, 0.45)	n/a
Wong 2022 molnupiravir	Hospitalisation	n/a	4,800/49,234 (9.75%)	476/4,983 (9.56%)	n/a	0.98 (0.90, 1.07)
	Death	n/a	734/49,234 (1.49%)	45/4,983 (0.91%)	n/a	0.61 (0.45, 0.82)
Yip 2023	Hospitalisation	177/4,921 (3.6%)	214/4,758 (4.5%)	249/4,798 (5.2%)	0.67[^] (0.55, 0.81)	1.17 [^] (0.99, 1.39)
	ICU admission, IMV use and/or death	20/4,921 (0.4%)	24/4,758 (0.5%)	29/4,798 (0.6%)	0.73 [^] (0.45, 1.49)	1.12 (0.68, 1.82)
Aggarwal 2023	Hospitalisation	61/7,168 (0.9%)	135/11,612 (1.4%)	n/a	0.45[^] (0.33, 0.62)	n/a
	Death	2/7,168 (0.02%)	15/11,612 (0.2%)	n/a	0.15[^] (0.03, 0.50)	n/a
Dryden-Peterson 2023	Hospitalisation within 14 days or death within 28 days	69/12,541 (0.55%)	310/32,010 (0.97%)	n/a	0.56 (0.42, 0.75)	n/a

Study (and subgroup)	Endpoint	Nirmatrelvir and ritonavir n/N (%)	Placebo n/N (%)	Molnupiravir n/N (%)	RR nirmatrelvir and ritonavir vs placebo (95% CI)	RR molnupiravir vs placebo (95% CI)
Ganatra 2023	ER visit, hospitalisation or death	89/1,130 (7.87%)	163/1,130 (14.4%)	n/a	0.55 (0.43, 0.70)	n/a
Kaboré 2023	Hospitalisation	299/8,402 (3.6%)	966/8,402 (11.5%)	n/a	0.31 (0.28, 0.36)	n/a
Lewnard 2023	Hospitalisation or death	51/7,274 (0.7%)	695/126,152 (0.55%)	n/a	1.27 [#] (0.96, 1.69)	n/a
Van Heer 2023	Hospitalisation	295/5,250 (5.6%)	1,635/13,721 (11.9%)	696/19,962 (3.5%)	0.60[^] (0.43, 0.83)	0.71[^] (0.58, 0.87)
	Death	29/5,250 (0.6%)	462/13,721 (3.4%)	346/19,962 (1.7%)	0.27[^] (0.18, 0.38)	0.45[^] (0.39, 0.53)

Sources: Constructed during the evaluation using CSRs and published reports of the studies. Table 14.2.1.3 of the EPIC-HR CSR, Table 15 of the EPIC-SR CSR, Table 2.6.4 of the submission, Figure 2 of Attachment 3 to the submission, Table 3 of Attachment 3 to the submission.

Abbreviations: CI = confidence interval; n= number with the event; N = total number in the analysis set; n/a = not applicable; NR = not reported; RR = relative risk

Bold font indicates statistical significance

* Subgroup is the subgroup of patients who were randomised prior to 21 January 2022, were vaccinated and had at least one risk factor.

[^]Adjusted hazard ratio. Denotes adjusted odds ratio for Aggarwal 2023 and Van Heer 2023

[#]Unadjusted

6.26 Although the PBAC has previously noted issues with respect to the applicability of evidence from EPIC-HR trial to the PBS population due to the majority of patients being unvaccinated at the time of the trial and due to the uncertain impact of differences in circulating variants of the virus, the randomised trials for nirmatrelvir and ritonavir are relevant to the assessment of the potential benefits and harms. The PBAC noted that the latest ATAGI update reported that only 53% of adults ≥65 years have had a booster dose in the last 6 months and that the vaccine efficacy declines significantly beyond three months⁹.

6.27 The submission also presented analyses examining time to hospitalisation, time to sustained alleviation of signs and symptoms of COVID-19, and time to sustained resolution of signs and symptoms of COVID-19.

6.28 The pre-PBAC response stated that the available evidence base for the treatment effect of Paxlovid is heterogeneous, and of variable quality and applicability to the next phase of the COVID-19 pandemic. The response maintained that a meta-analysis would provide the best estimate of future effectiveness.

Published meta-analyses

6.29 The submission presented two meta-analyses comparing nirmatrelvir and ritonavir to placebo (Amani 2023 and Cheema 2023). The results from the meta-analyses were used to inform the relative risks reflecting the treatment effect of nirmatrelvir and

⁹ ATAGI Update on the COVID-19 Vaccination Program, published 1 September 2023. <https://www.health.gov.au/news/atagi-update-on-the-covid-19-vaccination-program>.

ritonavir in the economic analyses and were thus critical to the submission. The meta-analyses reported by Amani 2023 included a broader range of studies than were included in the meta-analysis reported by Cheema 2023 but did not differentiate randomised controlled trials from observational studies and results from EPIC-SR are not included in the analyses.

- 6.30 The key results from the meta-analyses are reasonably consistent as can be seen from Figure 1 to Figure 3. As can be seen from these figures, the treatment effect of nirmatrelvir and ritonavir on rates of hospitalisation and on mortality in the observational studies is, generally, less than was observed in the randomised trials (i.e., the relative risks are generally higher in the observational studies). Furthermore, the results from the meta-analyses implicitly suggest that a different treatment effect is applicable for nirmatrelvir and ritonavir for the endpoint of hospitalisation than is applicable for the endpoint of death.
- 6.31 The randomised clinical trials of nirmatrelvir and ritonavir were not powered to be able to detect differences in the mortality component of the composite endpoint of hospitalisation or death through Day 28. The evaluation considered it doubtful that evidence from observational studies should be considered adequate for the purposes of deriving differential estimates of treatment effect to be applied in the economic analysis.
- 6.32 As discussed in paragraphs 6.64, 6.68, 6.70, and 6.73, the results of the economic analysis were sensitive to variables impacting rates of death in the cohort, including relative risk of death in patients treated with nirmatrelvir and ritonavir (rather than placebo).
- 6.33 A respecified base case was conducted during the evaluation that applied a relative risk of 0.30 for death (and for hospitalisation) for patients treated with nirmatrelvir and ritonavir compared with placebo, in place of the differential estimates of treatment effect proposed by the submission (Table 15). The estimated RR of 0.30 for death (and for hospitalisation) seems plausible given the range of results presented in Table 11 and Figures 1 to 3, with reference to the results from the EPIC-HR trial and the subgroup of the EPIC-SR trial, and given the observation from the observational studies of reduced treatment effect in practice compared to the randomised trials.
- 6.34 The PSCR claimed that the model’s approach to estimating deaths independent of hospitalisation is “logically correct and appropriate” because some patients, particularly in rural and remote areas die before being admitted to hospital. The ESC noted that no evidence to support or quantify this claim was presented. The ESC agreed with the commentary that based on the evidence available, it was reasonable to model death occurring in hospitalised patients, such that a single estimate of treatment effect for hospitalisation or death would be applicable. The ESC noted that the submission had not provided evidence to support a different approach, for example to estimate a proportion of deaths in non-hospitalised patients. The ESC requested that the sponsor provide evidence for this estimate if available, however

none was provided in the pre-PBAC response. The pre-PBAC response maintained that the approach taken in the submission was appropriate, as not all COVID-19 deaths occur in hospitalised patients, in particular in rural and remote areas, residential care facilities, or where hospital capacity is constrained.

- 6.35 The meta-analyses of the subset of randomised trials reported by Cheema 2023 (see Figure 2 and Figure 3) could be considered to appropriately capture the extent of uncertainty around point estimates of relative risk for hospitalisation and death. The ESC noted that estimates of treatment effect in some of the studies did not reach statistical significance. The ESC considered that, overall, the treatment effect of nirmatrelvir and ritonavir in practice appeared to be less than what was expected at the time it was recommended for listing on the PBS based on the results of EPIC-HR.
- 6.36 The ESC noted that the estimates of relative risk for hospitalisation and death were derived from meta-analyses that combined outcomes from randomised controlled trials with those from retrospective cohort studies and considered this was not appropriate, because observational studies involve further variability which is not accounted for in standard meta-analysis methods. While it may be possible to adjust for variability with statistical methods, it remained difficult to determine the role of selection bias or any confounding that the observational studies were suffering from in this instance.

Figure 1: Results of meta-analysis of key outcomes as reported by Amani 2023

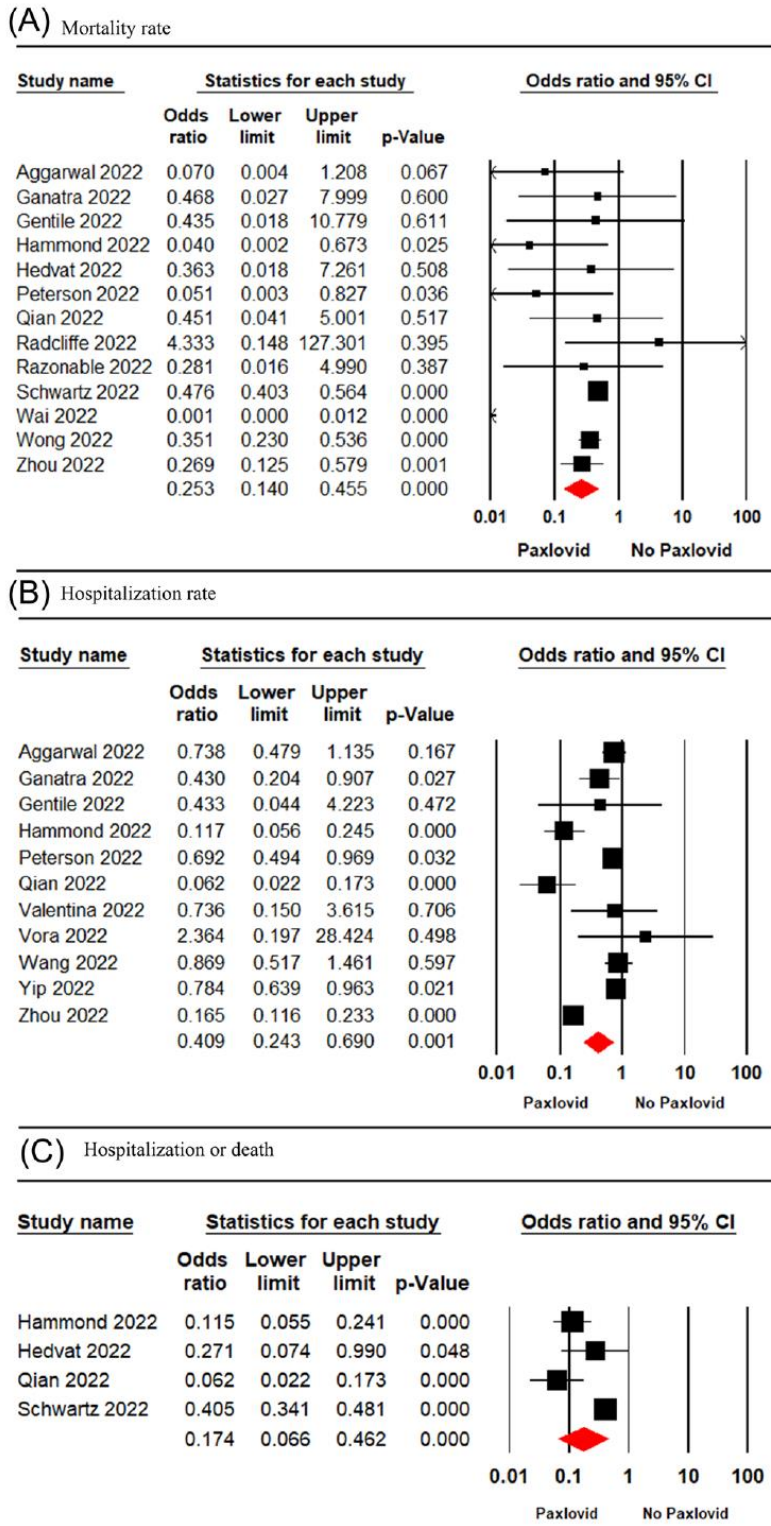


Figure 2: Results of meta-analysis of treatment effect of nirmatrelvir and ritonavir on risk of mortality as reported by Cheema 2023

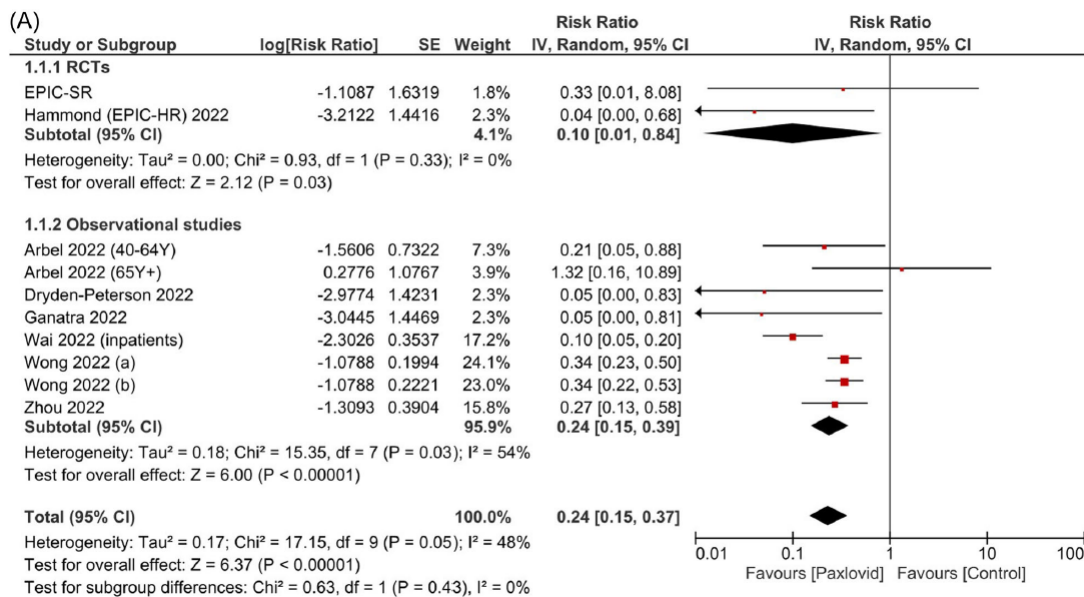
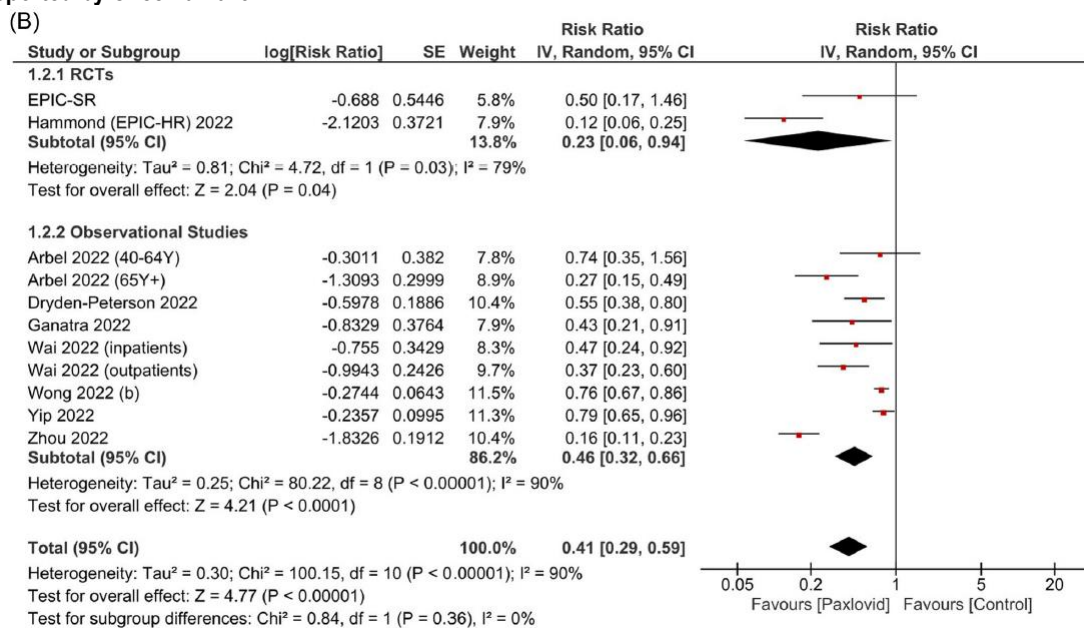


Figure 3: Results of meta-analysis of treatment effect of nirmatrelvir and ritonavir on risk of hospitalisation as reported by Cheema 2023

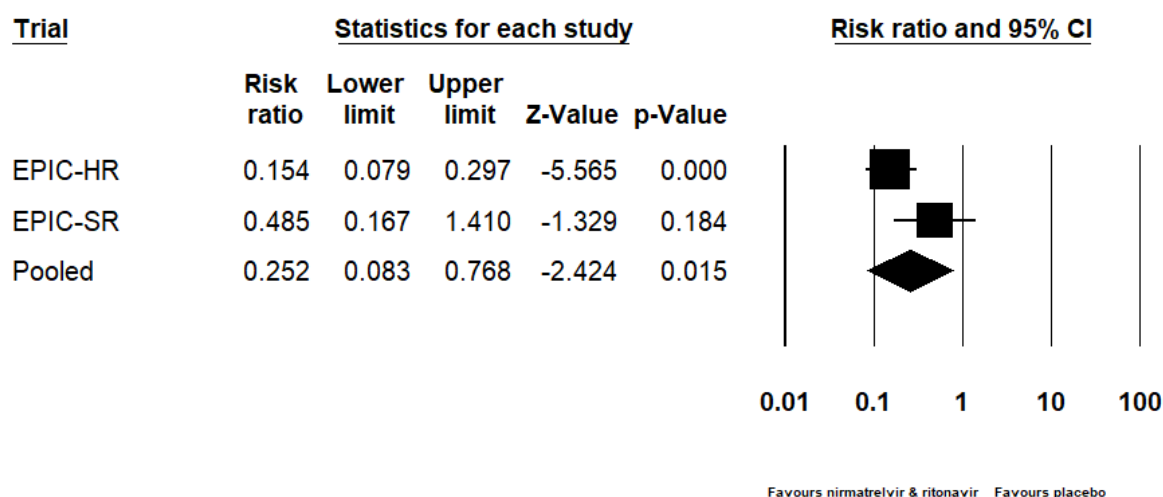


Meta-analyses conducted during the evaluation

6.37 A meta-analysis of results (risk ratios) for the composite endpoint of hospitalisation or death from the nirmatrelvir and ritonavir trials (EPIC-HR and EPIC-SR) is presented in Figure 4 (ITT populations). A second meta-analysis of results (risk ratios) is presented for EPIC-HR and the high risk patients from EPIC-SR in Figure 5 (reflecting high-risk

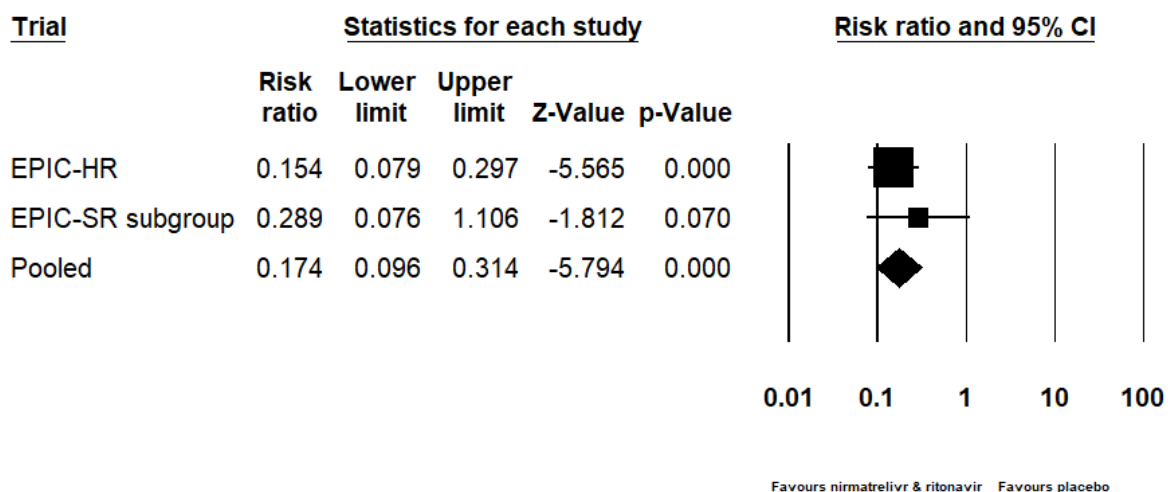
patients in the RCTs). The meta-analyses are also presented as odds ratios, in Figure 6 (ITT) and Figure 7 (high risk).

Figure 4: Meta-analysis of results (risk ratios) for the composite endpoint of hospitalisation or death from the nirmatrelvir and ritonavir trials (EPIC-HR and EPIC-SR)



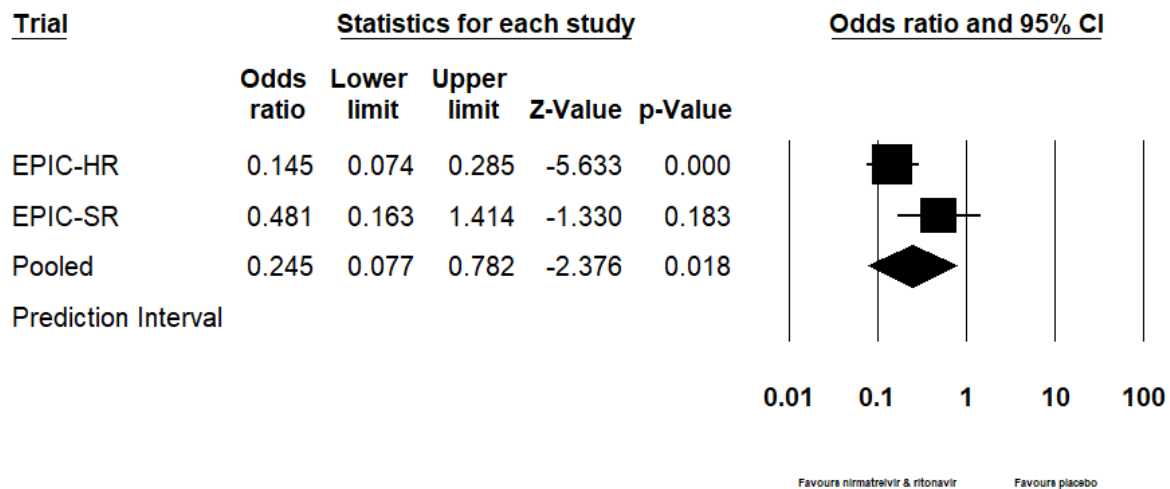
Source: Conducted during the evaluation. Data sources for raw numbers permitting calculation of risk ratios: Table 14.2.1.3 of the EPIC-HR CSR (10/1038 in the nirmatrelvir and ritonavir arm and 66/1053 in the placebo arm), Table 15 of the EPIC-SR CSR (5/654 in the nirmatrelvir and ritonavir arm and 10/634 in the placebo arm), see Table 11.

Figure 5: Meta-analysis of results (risk ratios) for the composite endpoint of hospitalisation or death from the nirmatrelvir and ritonavir trials (EPIC-HR and the high risk subgroup from EPIC-SR)



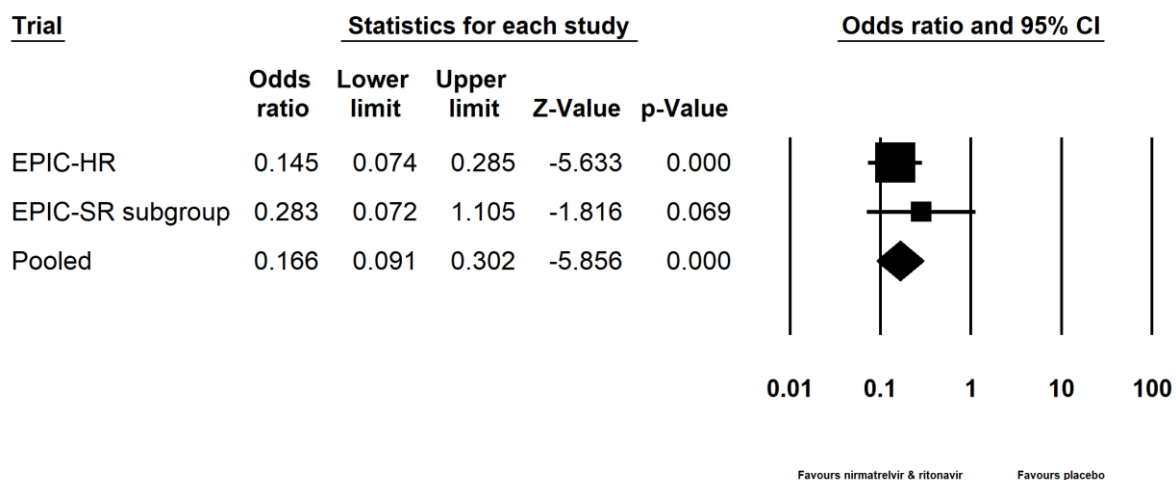
Source: Conducted during the evaluation. Data sources for raw numbers permitting calculation of risk ratios: Table 14.2.1.3 of the EPIC-HR CSR (10/1038 in the nirmatrelvir and ritonavir arm and 66/1053 in the placebo arm), Table 17 of the EPIC-SR CSR (3/317 in the nirmatrelvir and ritonavir arm and 7/314 in the placebo arm)

Figure 6: Meta-analysis of results (odds ratios) for the composite endpoint of hospitalisation or death from the nirmatrelvir and ritonavir trials (EPIC-HR and EPIC-SR)



Source: Conducted during the evaluation. Data sources for raw numbers permitting calculation of odds ratios: Table 14.2.1.3 of the EPIC-HR CSR (10/1038 in the nirmatrelvir and ritonavir arm and 66/1053 in the placebo arm), Table 15 of the EPIC-SR CSR (5/654 in the nirmatrelvir and ritonavir arm and 10/634 in the placebo arm)

Figure 7: Meta-analysis of results (odds ratios) for the composite endpoint of hospitalisation or death from the nirmatrelvir and ritonavir trials (EPIC-HR and the high risk subgroup from EPIC-SR)



Source: Conducted during the evaluation. Data sources for raw numbers permitting calculation of odds ratios: Table 14.2.1.3 of the EPIC-HR CSR (10/1038 in the nirmatrelvir and ritonavir arm and 66/1053 in the placebo arm), Table 17 of the EPIC-SR CSR (3/317 in the nirmatrelvir and ritonavir arm and 7/314 in the placebo arm)

Long COVID

6.38 Post-acute COVID-19 syndrome (PACS), also known as post-COVID syndrome (PCS), post-COVID condition, and long COVID (and referred to as long COVID hereafter) is a sequela of COVID-19 that can be characterised by symptom persistence for > 3 months, development of symptoms after the acute phase of COVID-19, and worsening of pre-existing comorbidities. As noted by the submission, following a referral on 1 September 2022 from the Minister for Health and Aged Care, the Hon Mark Butler MP, the House Standing Committee on Health, Aged Care and Sport inquired into and

reported on long COVID and repeated COVID infections. The Committee published its report 'Sick and tired: Casting a long shadow' on 24 April 2023¹⁰. The report highlighted that there is not, at present, an agreed definition of what constitutes long COVID and there is a poor understanding of the causes and predictors of long COVID. As discussed in paragraph 6.64, the modelled economic evaluation presented in the submission assumed a reduced incidence of long COVID in patients treated with nirmatrelvir and ritonavir. However, as acknowledged by the submission, the effectiveness of nirmatrelvir and ritonavir in preventing PACS was not reported by any of the published trials, studies or meta-analyses presented in the section of the submission that presented the clinical evidence. It was not reported that a systematic search of the literature was conducted to identify studies that examine the impact of treatment with nirmatrelvir and ritonavir on incidence of long COVID.

- 6.39 The assumption in the economic evaluation of a reduced incidence of long COVID following treatment was based on a single retrospective observational cohort study reported by Xie et al, 2023¹¹. This cohort study used the databases of the US Department of Veterans Affairs to identify patients with at least one risk factor for progression to severe COVID-19, who tested positive for SARS-CoV-2 in the period from 3 January 2022 to 31 December 2022, were treated with nirmatrelvir (n = 35,717) or received no COVID-19 antiviral or antibody treatment (n = 246,076) within 5 days of the positive test and survived the first 30 days after diagnosis of SARS-CoV-2 infection. The authors noted that nirmatrelvir is marketed in combination with ritonavir, however the cohorts were defined as nirmatrelvir group and control group. 13 post-acute sequelae (ischaemic heart disease, dysrhythmia, deep vein thrombosis, pulmonary embolism, fatigue and malaise, liver disease, acute kidney injury, muscle pain, diabetes, neurocognitive impairment, dysautonomia, and shortness of breath and cough) were given weights and the sum of the weights of incident sequelae over the period of follow up was generated. A propensity score for being prescribed nirmatrelvir was derived based on data collected in the period before the study period. Inverse probability weights were applied to the control group to estimate the association within a population with the same baseline characteristics as the nirmatrelvir. Xie et al, (2023) estimated that compared with untreated patients, nirmatrelvir reduced PACS risk by 26% (RR=0.74; 95% CI: 0.72-0.77).
- 6.40 The ESC noted that a quick search of the literature conducted during the evaluation identified reports of two studies that investigated whether nirmatrelvir and ritonavir reduced the risk of long COVID 19. Neither of the studies found that nirmatrelvir and ritonavir reduced the risk of long COVID:

¹⁰ House of Representatives Standing Committee on Health, Aged Care and Sport. Sick and tired: Casting a long shadow. April 2023

¹¹ Xie, Y., T. Choi, and Z. Al-Aly. 2023. "Association of Treatment With Nirmatrelvir and the Risk of Post-COVID-19 Condition." *JAMA Intern Med.* doi: 10.1001/jamainternmed.2023.0743.

- A pre-print article by Durstenfeld 2023¹² reported results from an observational study funded by the Bill & Melinda Gates Foundation that examined outcomes in 4,684 individuals experiencing their first known SARS-CoV-2 infection and investigated whether those treated with nirmatrelvir and ritonavir reported lower rates of long COVID compared to untreated patients. The authors report that they “did not find evidence that treatment with oral nirmatrelvir/ritonavir during the acute phase of COVID-19 was associated with a lower prevalence of patient-reported Long COVID symptoms at least 90 days after infection among vaccinated, non-hospitalized individuals experiencing their first known SARS-CoV-2 infection”.
 - Similarly, Chuang 2023¹³ reported the results of a retrospective cohort study that examined the risk of post-acute symptoms in 24,490 patients treated with either nirmatrelvir and ritonavir or were untreated and found that the overall risk of post-acute COVID-19 symptoms did not significantly differ between the two groups.
- 6.41 The ESC noted that the submission did not appear to have conducted a systematic search of the literature, instead relying on a single publication (Xie et al, 2023). The ESC noted the potential for Xie et al to be a biased representation of the evidence, with high potential for confounded results due to its observational study design. The ESC did not consider that Xie et al constituted an adequate basis for claiming that nirmatrelvir and ritonavir reduces the incidence of long COVID.
- 6.42 The PBAC noted that an additional study based on U.S. Department of Veterans Affairs (VA) data was published by Ioannou et al on 31 October 2023¹⁴, which reported results that differed from those of the study by Xie and colleagues. The authors reported that nirmatrelvir and ritonavir was not effective at reducing the risk for many of the post-COVID-19 conditions (PCCs) after acute infection that were examined compared with no treatment, including cardiac, pulmonary, renal, gastrointestinal, neurologic, mental health, musculoskeletal, endocrine, and general conditions and symptoms. The study found that out of 31 potential PCCs, that nirmatrelvir and ritonavir was associated only with a reduced risk for combined thromboembolic events. The authors reported that given the large number of outcomes assessed, the observed association between nirmatrelvir and ritonavir treatment and lower incidence of combined thromboembolic events could have arisen by chance.

¹² Durstenfeld M, et al 2023. Association of Nirmatrelvir/Ritonavir Treatment with Long COVID Symptoms in an Online Cohort of Non-Hospitalized Individuals Experiencing Breakthrough SARS-CoV-2 Infection in the Omicron Era (Preprint) medRxiv 2023.03.02.23286730; doi: <https://doi.org/10.1101/2023.03.02.23286730>

¹³ Chuang, M-H, Wu, J-Y, Liu, T-H, et al. Efficacy of nirmatrelvir and ritonavir for post-acute COVID-19 sequelae beyond 3 months of SARS-CoV-2 infection. *J Med Virol.* 2023; 95:e28750. doi:10.1002/jmv.28750

¹⁴ Ioannou GN, et al. Effectiveness of Nirmatrelvir-Ritonavir Against the Development of Post-COVID-19 Conditions Among U.S. Veterans : A Target Trial Emulation. *Ann Intern Med.* 2023 Oct 31: doi: 10.7326/M23-1394. Epub ahead of print.

Comparative harms

- 6.43 Of the trials and studies presented in the submission, the EPIC-HR and EPIC-SR trials assessed safety of nirmatrelvir and ritonavir. However, the submission did not present safety results from these trials.
- 6.44 The analysis of adverse events (AEs) in the EPIC-HR trial indicated that nirmatrelvir and ritonavir is generally well tolerated, with 22.0% of nirmatrelvir and ritonavir-treated patients and 24.3% of placebo-treated patients experiencing adverse events (any grade). Serious adverse events were observed in 1.7% of the nirmatrelvir and ritonavir-treated group and in 6.7% of the placebo-treated group. The most frequently reported AEs (occurring in $\geq 1\%$ of participants in either group, reported as nirmatrelvir and ritonavir-treated patients vs. placebo-treated patients) excluding AEs related to investigations and due to infection were dysgeusia (4.6% vs 0.1%), headache (1.2% in both arms), diarrhoea (3.0% vs. 1.5%), nausea (1.4% vs. 1.8%), and vomiting (1.2% vs 0.9%).
- 6.45 Safety results from the EPIC-SR trial were consistent with those reported for the EPIC-HR trial. 25.8% of nirmatrelvir and ritonavir-treated patients and 24.1% of placebo-treated patients experienced adverse events (any grade). Serious adverse events were observed in 1.2% of the nirmatrelvir and ritonavir-treated group and in 1.9% of the placebo-treated group. The most frequently reported AEs (occurring in $\geq 1\%$ of participants in either group, reported as nirmatrelvir and ritonavir-treated patients vs. placebo-treated patients) excluding AEs related to investigations and due to infection were dysgeusia (6.7% vs 0.5%), headache (0.9% vs 1.3%), diarrhoea (4.0% vs. 3.0%), dyspepsia (1.2% vs 0.3%), nausea (3.1% vs. 2.7%), and vomiting (1.7% in both arms).
- 6.46 The submission provided a Periodic Safety Update Report (PSUR) with reporting period from 31 December 2021 to 30 Jun 2022. Evaluation of information during the reporting period did not identify any additional clinically relevant new safety information.
- 6.47 The submission provided a summary of the post-marketing safety study reported by Zhuang et al, 2023. However, the published report was not provided with the submission. The study identified disease recurrence, dysgeusia, diarrhoea, nausea, headache and vomiting as the main safety signals associated with nirmatrelvir and ritonavir. Notably, the highest safety signal reported by Zhuang et al, 2023 was disease recurrence (rebound effect), which was reported at a rate of 18.78%.
- 6.48 In some patients treated with antivirals, rebound of viral load and recurrence of symptoms after completion of a 5-day antiviral treatment has been observed in practice. This phenomenon is referred to as the rebound effect. The mechanism driving rebound is not yet understood though hypotheses are appearing in the literature (e.g., a preprint by Perelson et al, 2023 suggests that initiation of treatment close to the time of symptom onset may interfere with the strength and timing of innate adaptive immune response).

6.49 The DUSC Secretariat conducted an analysis of PBS utilisation of antiviral treatments for COVID-19 that investigated the proportion of patients having a second prescription for an antiviral dispensed within 30 days of dispensing of the original prescription for an oral antiviral. The key results of this analysis are summarised in Table 12. Although the proportion of patients having a second prescription for an oral antiviral dispensed within 30 days of dispensing of an initial antiviral is low, it is likely that the proportion of patients having a second prescription dispensed within 30 days will be an underestimate of the proportion of patients experiencing rebound COVID as it is probable that a substantial proportion of patients would not have a second prescription for an antiviral dispensed despite experiencing rebound symptoms. The relative risk (RR) of prescribing of a second antiviral within 30 days of an initial prescription was significantly higher in patients initially treated with nirmatrelvir and ritonavir than in patients initially treated with molnupiravir (RR: 1.64; 95% CI: 1.57 – 1.71). The ESC noted that in some instances a second prescription may be issued for a patient experiencing side effects to the first antiviral.

Table 12: Patients commencing on an oral antiviral treatment and receiving a second prescription for an oral antiviral treatment within 30 days in the period through to 30 June 2023

Initial treatment dispensed	Initiating patients	Patients receiving a second prescription for an antiviral treatment <30 days	Proportion
Molnupiravir	608,972	4,845	0.80%
Nirmatrelvir and ritonavir	271,712	3,535	1.30%
Totals:	880,684	8,380	0.95%

Source: Analysis provided by DUSC Secretariat, 31 July 2023.

6.50 The PSCR cited a letter to the editor published at NEJM.org, reporting on viral load rebound in EPIC-HR (Anderson 2022¹⁵). The PSCR stated that in the EPIC-HR trial, COVID-19 recurrence as defined by prespecified criteria for viral load rebound (i.e., a half-log increase in viral load on Day 10 and/or Day 14) was used to identify patients resistant to nirmatrelvir. From baseline through Day 14, viral load rebound occurred in 2.3% of patients treated with Paxlovid (n=23/990) and 1.7% of patients in the placebo group (n=17/980). The PSCR stated that incidence of viral load rebound was similar among the two cohorts, irrespective of presence of coexisting illnesses, nirmatrelvir exposure, the recurrence of moderate-to-severe COVID-19 symptoms, SARS-CoV-2 serologic status at baseline, nirmatrelvir resistance and importantly, the occurrence of hospitalisation or death (Anderson 2022). The PSCR also reported outcomes from two cohort studies conducted in Hong Kong suggesting viral rebound was uncommon in patients treated with nirmatrelvir and ritonavir or molnupiravir (Wong 2022, Wong 2023). These studies were limited to patients hospitalised for COVID-19 and are thus of limited relevance to the PBS population. The PSCR also referenced a meta-analysis reported by Zheng 2023 of 3 observational studies reporting incidence of rebound, 2 of which were conducted in hospitalised patients.

¹⁵ Anderson AS, Caubel P, Rusnak JM; EPIC-HR Trial Investigators. Nirmatrelvir-Ritonavir and Viral Load Rebound in Covid-19. N Engl J Med. 2022 Sep 15;387(11):1047-1049. doi: 10.1056/NEJMc2205944. Epub 2022 Sep 7.

The ESC considered that neither the submission nor the PSCR adequately discussed the potential for rebound COVID after treatment with nirmatrelvir and ritonavir.

Benefits/harms

- 6.51 On the basis of evidence from the EPIC-HR trial, for every 100 patients treated with nirmatrelvir and ritonavir in comparison with placebo:
- approximately 5 fewer patients would experience hospitalisation or death within 4 weeks.
- 6.52 On the basis of evidence from the EPIC-SR trial, for every 100 patients treated with nirmatrelvir and ritonavir in comparison with placebo:
- no difference in hospitalisations or deaths within 4 weeks.

Clinical claim

- 6.53 The submission described nirmatrelvir and ritonavir as superior in terms of effectiveness compared to placebo (representing no antiviral treatment). The ESC considered that a claim of superiority was supported for high risk patients, including vaccinated patients, however, the data were less convincing for patients at lower risk of developing severe COVID 19.
- 6.54 The submission described nirmatrelvir and ritonavir as similar in terms of safety compared to placebo (representing no antiviral treatment). This claim was poorly supported. The ESC considered that, although nirmatrelvir and ritonavir was generally well tolerated, the incidence of dysgeusia was statistically significantly higher in patients treated with nirmatrelvir and ritonavir than in placebo-treated patients in both the EPIC-HR and EPIC-SR trials.
- 6.55 The submission did not make any claims regarding the comparative effectiveness of nirmatrelvir and ritonavir versus molnupiravir.
- 6.56 The PBAC considered that the submission's claim of superior effectiveness compared with placebo was supported by the data.
- 6.57 The PBAC considered that the submission's claim of similar safety compared with placebo was reasonable.

Economic analysis

- 6.58 The submission presented five cost-utility analyses that compared costs and quality-adjusted survival over a lifetime in patients treated with:
- nirmatrelvir and ritonavir
 - molnupiravir
 - placebo (representing no antiviral treatment)

6.59 Base case cost-utility analyses reported in the submission were reported as being for four mutually exclusive populations that were intended to represent the populations covered by each of the restrictions listed in Table 4 to Table 7:

- Persons aged ≥ 70 years;
- Persons aged ≥ 18 years who are moderately to severely immunocompromised or had previously required hospitalisation for COVID-19;
- Aboriginal or Torres Strait Islander people aged ≥ 30 years with one or more risk factors (with prior hospitalisation for COVID-19 included as risk factor);
- people aged 50 - 69 years with one or more risk factors.

A weighted incremental cost-effectiveness ratio (ICER) for the total population was calculated as scenario analysis.

There was a discrepancy between the description of the population in this base case and the Excel workbook provided with the submission. Specifically, the model in the Excel workbook provided with the submission did not include patients aged 50 – 59 with only one additional risk factor. A second model was constructed during the evaluation to derive results that were consistent with those reported in the submission. Details presented in this document that aligned with the results presented in the submission rather than the workbook provided with the submission.

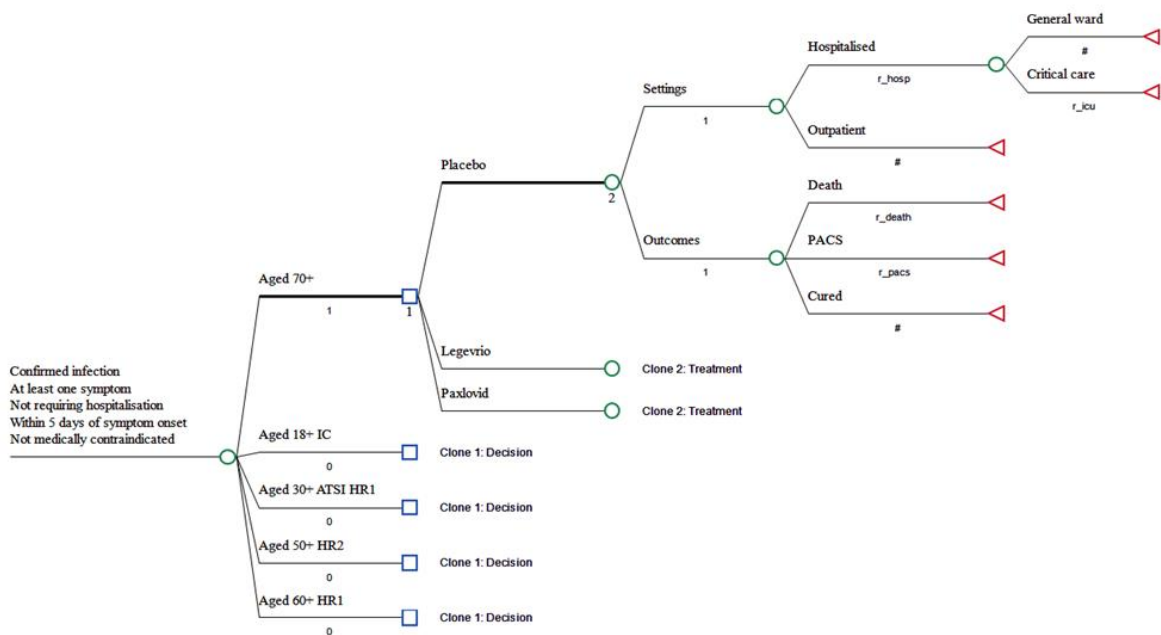
6.60 The fifth cost-utility analysis was for a scenario analysis that reverted the fourth population listed above to the population that was eligible prior to the extension recommended in June 2023 of the listing to include patients aged 50-59 with only one additional risk factor (i.e. the scenario includes patients aged 50-59 with at least two additional risk factors). Similarly, the submission reported a scenario that reverted the fourth population above to the criteria prior to 1 April 2023 (i.e. includes patients aged 50-69 with at least two additional risk factors). An analysis for the population of patients that was eligible for treatment with nirmatrelvir and ritonavir as at 1 February 2023 (i.e., limiting availability for people aged 50 – 69 years to those with two or more additional risk factors [patients who had < 2 additional risk factors but who required hospitalisation for COVID-19 would be eligible under the restriction for people aged ≥ 18 years who are either moderately to severely immunocompromised with risk of progression to severe COVID-19 disease or have experienced past COVID-19 infection resulting in hospitalisation]) was conducted during the evaluation applying baseline risks for patients aged 60 – 69 years with two or more additional risk factors as reported for this population in the sensitivity analyses.

6.61 The submission recognised that although the approach of splitting the population into different cohorts is technically appropriate, there are multiple problematic issues associated with the application of currently available epidemiological and clinical trial evidence. Examples of issues that are problematic include: all published evidence relates to historical strains of the virus and levels of vaccine- or natural immunity; heterogeneity in the literature regarding baseline risks of events and impact of

antiviral treatment on those risks; and populations examined by studies are frequently not specific to populations for whom continued listing of nirmatrelvir and ritonavir is sought. These issues contribute to uncertainty in the estimates of cost-effectiveness generated by any economic analysis conducted of treatments for COVID-19.

6.62 Figure 8 presents the fundamental structure of the model used to conduct the cost-utility analyses presented in the submission. The model was implemented in a straightforward Microsoft Excel workbook. Table 13 summarises the key features and inputs to the modelled cost-utility analyses presented in the submission.

Figure 8: Structure of the model presented in the submission



Source: Figure 3.2.1 on p180 of the submission

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Nirmatrelvir and ritonavir versus molnupiravir vs placebo (for no use of antivirals) All treatments are assumed to be administered at recommended doses in accordance with the PBS restrictions
Time horizon	Lifetime
Outcomes	Quality-adjusted survival
Methods used to generate results	Cohort expected value decision analysis
Payoff states captured by the decision analysis	Three settings for management of patients are considered <ul style="list-style-type: none"> • Management in the outpatient setting • Hospitalisation without need for critical care admission (≤ 28 days) • Hospitalisation with critical care admission Three possible long term outcomes are considered following management of COVID-19 <ul style="list-style-type: none"> • Cured (full recovery) • Long COVID (average duration 90 days) • COVID-19 related death (≤ 180 days) The above events and outcomes are used to derive QALYs lost to COVID-19
Cycle length	Not applicable in a decision analysis
Probabilities	Baseline mortality and morbidity event risks applied in the placebo arm of the model were estimated from published epidemiological studies and supporting information (see paragraph 6.63). Relative risks of these events in patients treated with nirmatrelvir and ritonavir or molnupiravir were estimated from meta-analyses of outcomes observed in clinical trials and observational studies (see paragraph 6.64).
Extrapolation method	QALYs lost per fatal case of COVID-19 are estimated by application of a discounted quality adjusted life expectancy (dQALE) based on the characteristics of the cohort being modelled (see paragraph 6.65).
Health related quality of life	The literature on the impact of acute COVID-19 and long COVID was considered to be immature. Estimates of utility decrements by health state were estimated based on a broad review of the literature and analyst judgement (see paragraph 6.66)

Sources: Table 3.1.1 on p175 of the submission, Sections 3.5.1 and 3.5.2 of the submission

6.63 The baseline risk of events applied in the economic analyses are summarised in Table 14.

- Total proportions of patients hospitalised for COVID-19 in each arm of the model (including those requiring critical care) were estimated by the submission to be between 1.5% and 5%. The estimates were not based on any particular data source but were based on a consideration of a range of data sources including clinical opinion. The submission acknowledged that there is considerable uncertainty in the estimates applied in the economic analysis and expressed the sponsor's willingness to consider alternative estimates. The estimates of proportion of patients requiring hospitalisation may be appropriate however the structure of the model meant that death was applied as a separate, independent parameter in the economic analysis.
- The proportion of patients dying in each arm was estimated by the submission to be between 1% and 3% of cases. The estimates were not based on any particular data source but were estimated based on a consideration of a range of data sources. The submission acknowledged that there was considerable uncertainty in the estimates applied in the economic analysis and expressed the sponsor's

willingness to consider alternative estimates. The ESC considered that some of the background rates of mortality applied in the model seemed high, particularly for a vaccinated population, and agreed with the commentary that these should be reviewed. The rates of death are higher than observed in any of the clinical trials conducted in high risk patients who were unvaccinated and were conducted at a time when more pathogenic variants were circulating. The mortality rates in the placebo-treated high-risk groups of the EPIC-HR and MOVE-OUT trials were 1.1% (12/1051) and 1.3% (9/699), respectively. If it is assumed that the vast majority of deaths occur in hospitalised patients, the case fatality rates for hospitalised patients implicitly applied in the economic analysis are extremely high. Macedo et al, 2021¹⁶ reported the results of a systematic review of case fatality rates in hospitalised patients between December 2019 and April 2021 and estimated mortality rates of approximately 11% for general patients in hospital and 41% for patients requiring critical care. These rates reflect mortality rates in the initial phase of the pandemic prior to availability of vaccines and treatments for COVID-19. In summary, estimates applied in the model were at least three times higher than reported in the EPIC-HR trials and in Macedo et al, 2021. On this basis, the commentary presented respecified base case analyses assuming mortality rates were 33% of those assumed in the submission's base case as shown in Table 20. The PSCR disagreed with the reduction in baseline mortality applied in the respecified base case economic analysis. The ESC noted, as discussed in the Commentary, the submission's model assumed a death rate of between 0.75% and 3%, which resulted in implausibly high implied case fatality rates for hospitalised patients, when it assumed that all deaths occur in hospitalised patients (Table 14).

- As discussed in paragraph 6.38, and as shown in Figure 8 and Table 13, the submission assumed an impact of treatment on the incidence of long COVID. Based on the report of the House Standing Committee on Health, Aged Care and Sport's inquiry into long COVID and repeated COVID infections and a published review of the literature for long COVID, the submission estimated a baseline incidence of long COVID of 10% for application in each of the analyses¹⁷. This estimate appeared reasonable. Discussion of the assumption of treatment effect of nirmatrelvir and ritonavir on long COVID is provided at paragraphs 6.38 to 7.16.

¹⁶ Macedo A, Gonçalves N, Febrá C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. *Ann Epidemiol.* 2021;57:14-21. <https://doi.org/10.1016/j.annepidem.2021.02.012>

¹⁷ Davis H et al. Long COVID: major findings, mechanisms and recommendations. *Nature reviews microbiology* Volume 21 MRCH 2023. <https://doi.org/10.1038/s41579-022-00846-2>

Table 14: Baseline risk of events applied in the economic model

Population	Event				
	Hospitalisation in a general ward only	Hospitalisation including admission to critical care unit	Death	Implied case fatality rate for hospitalised patients if all deaths occur in hospitalised patients	Long COVID
Aged ≥ 70	4.50%	0.50%	3.00%	60%	10%
Aged ≥18 and immune-compromised*	3.60%	0.40%	3.00%	75%	10%
Indigenous aged ≥ 30 and ≥ 1 risk factor	2.70%	0.30%	2.00%	67%	10%
Aged 50-59 & ≥ 2 risk factors	1.90%	0.10%	1.00%	50%	10%
Aged 60-69 & ≥ 1 risk factor	1.90%	0.10%	1.00%	50%	10%
Aged 60-69 & ≥ 2 risk factors	2.375%	0.125%	1.50%	60%	10%
Aged 50-69 & ≥ 1 risk factor	1.425%	0.075%	0.75%	33.3%	10%

Source: Revised model constructed during the evaluation

* assumed to include patients aged ≥18 previously requiring hospitalisation for COVID-19

6.64 Table 15 summarises the assumed relative risks of events for patients treated with nirmatrelvir and ritonavir or molnupiravir in the model. There was an inconsistency between the relative risk reported to be applied in the model (Table 3.4.3 of the submission) and those actually applied in the model. The Commentary assumed this to be a transcription error, Table 15 reports the relative risks actually applied in the model.

- As discussed in paragraph 6.38, the economic evaluation assumed a treatment effect of the antivirals on the incidence of long COVID but the evidence supporting such an assumption is weak and an inadequate basis for establishing that nirmatrelvir and ritonavir reduces the incidence of long COVID. Respecified base case analyses removing this treatment effect are presented in Table 20.
- The source of the treatment effects applied in the modelled economic analysis for hospitalisation and death were the meta-analyses discussed at paragraph 6.29. As discussed in paragraph 6.29, the meta-analyses combine data from randomised controlled trials and observational retrospective cohort studies. The ESC considered this was not appropriate (see paragraph 6.36).
- Furthermore, as can be seen from Table 15, relative risks of events were assumed to vary depending on the event. The evaluation considered evidence for differential treatment effect by event to be weak. The primary endpoint of the clinical trials in high risk patients was a composite of hospitalisation and death and the proportions of patients dying in the randomised clinical trials were too small

to permit derivation of differential treatment effects. Estimates of treatment effect by event based on observational retrospective cohort studies will be associated with a high risk of bias. The respecified base case presented in Table 20 applied consistent relative risks of hospitalisation and death (0.30). The same RR (0.30) is applied to ICU admissions as it is a subset of hospitalisations.

- The same set of relative risks were applied regardless of the population (Table 15). This assumption may be appropriate given that the submission did not present evidence to support an assumption of treatment effect modification by population type. However with reference to EPIC-SR, as discussed in paragraph 6.25, neither the results based on the mITT1 population nor those for the prespecified subgroup analyses that restricted analysis to patients who were considered at high risk (defined as having at least one risk factor) reached statistical significance, in contrast to EPIC-HR. Thus, it could be considered inappropriate for the economic model to apply the same treatment effect to patients at lower risk of developing severe disease (e.g., patients aged 50 to 60 years with only one additional risk factor) that was applied to those at higher risk.

Table 15: Relative risk of events in patients treated with nirmatrelvir and ritonavir or molnupiravir

Event	Nirmatrelvir and ritonavir	Molnupiravir*
Hospitalisation	0.41	0.81
ICU (critical care) admission	0.37	0.75
Death	0.25	0.63
Long COVID	0.74	0.86

Source: Table 3.4.3 of the submission and the economic model presented with the submission

* Values reported for molnupiravir in Table 3.4.3 did not reflect values applied in the economic analysis. Values reported in this table are those applied in the economic analysis.

6.65 The submission estimated discounted quality adjusted life expectancies (dQALEs) for each of the modelled cohort, representing the QALY loss per fatal case of COVID-19. This estimate was combined with undiscounted short term QALY decrements (QALYd) associated with transient instances of acute COVID-19 or long COVID. The approach to derivation of the dQALEs applied in the model generally appeared reasonable however it may have been appropriate for the QALYs lost for patients aged 60 - 69 with ≥ 2 additional risk factors to have been less than for patients ≥ 1 risk additional factor. The QALYs lost by patients with fatal outcomes applied in each of the cohorts is summarised in Table 16.

Table 16: QALYs lost by patient who died by cohort

Population (cohort)	QALYs lost by patients who died
Aged ≥ 70	6.44
Aged ≥ 18 and immune-compromised*	15.57
Indigenous aged ≥ 30 and ≥ 1 risk factor	13
Aged 50-59 & ≥ 2 risk factors	12.18
Aged 60-69 & ≥ 1 risk factor	10.65
Aged 60-69 & ≥ 2 risk factors	10.65
Aged 50-69 & ≥ 1 risk factor	12.18

Source: Table 3.5.1 and Table 3.9.7 of the submission

* assumed to include patients aged ≥ 18 previously requiring hospitalisation for COVID-19

6.66 The submission stated that literature on the quality of life impact of acute COVID-19 and long COVID was immature. Estimates of utility decrements for patients experiencing events in the model were estimated based on a broad review of the literature and analyst judgement. In the absence of rigorous studies reporting quality of life in patients with COVID-19, the pragmatic approach adopted was reasonable. The disutilities applied, the duration in the health state and the total QALYs lost by patients in the various health states are summarised in Table 17. There was a typographical error in the reporting of the disutility in Table 3.5.2 of the submission, which has been corrected in Table 17.

Table 17: Disutilities applied to temporary states in the economic analysis

Event	Disutility	Duration	QALYs lost
Managed in the outpatient setting	0.2*	5	0.0027
Required admission to a general ward of a hospital	0.4	7	0.0077
Required admission to a critical care unit in a hospital	0.6	10	0.0164
Long COVID	0.2	90	0.0493

Source: Table 3.4.3 of the submission and the economic model presented with the submission

* Values reported for molnupiravir in Table 3.4.3 did not reflect values applied in the economic analysis. Values reported in this table are those applied in the economic analysis.

6.67 Health care resource use and costs associated with such use that were incorporated into the model include:

- **Drug costs:** The dispensed prices of nirmatrelvir and ritonavir or molnupiravir were included in the economic analysis. The cost applied for nirmatrelvir and ritonavir was the requested PBS DPMQ as specified in Section 1 (\$) of the submission. The cost applied for molnupiravir was the dispensed price for PBS Item 12910L as at 6 June 2023 (\$1,101.39). No drug costs were included for treatment of patients in the placebo arm.
- **Medical care:** It was assumed that all patients prescribed an antiviral would have had a brief telehealth consultation (MBS Item 91890L) for eligibility assessment and prescribing of antiviral medication. It was assumed that 50% of patients in the placebo arm would have had a telehealth consultation. The ESC noted that the assumption that patients on multiple medications could be assessed and prescribed nirmatrelvir and ritonavir in a 6-minute telephone consultation was unlikely to be valid. Thus, the costs of medical care may be underestimated.
- **Hospitalisation:** In the absence of validated Australian data available in the public domain reporting the average cost of managing acute cases of COVID-19 infection among high risk patients in a general ward or ICU setting, costs from the National Hospital Cost Data Collection (Public Sector, Round 23, 2018-2019) were applied. Specifically, weighted (by separation) average costs for AR-DRG items E62 A/B (Respiratory Infections and Inflammations) and E40/41 A/B (Respiratory System Disorders with Ventilator Support / Respiratory System Disorders with Non-Invasive Ventilation) have been used respectively, for episodes of treatment in a general ward (\$6,419) or ICU (\$20,675) setting.

- Costs associated with the management of long COVID were estimated by application of a cost to manage chronic fatigue syndrome (as reported by Vos-Vromans et al, 2017) as a proxy for costs to manage long COVID. The approach resulted in an estimate of \$3,586 per case of long COVID in the model.

6.68 Table 18 summarises the key drivers of the outcomes generated by the model as demonstrated by sensitivity analyses presented in Table 21. The key drivers of outcomes generated by the model are: baseline risk of death; the relative risk of death in patients treated with nirmatrelvir and ritonavir; and the QALYs assumed to be lost by patients who die in the acute phase of COVID-19. Each of these inputs have a direct impact on patients dying in the model (either the proportion of patients dying or the QALYs lost through death). As shown in Table 21, the results of the economic analyses are very sensitive to the inputs.

Table 18: Key drivers of the outcomes generated by the economic analyses

Description	Method/Value	Impact
Baseline risk of death due to COVID-19	Derived based on a consideration of a range of sources 0.75% to 3%	High, a high value favours nirmatrelvir and ritonavir
Relative risk of death with nirmatrelvir and ritonavir treatment	Derived based on meta-analyses that combined outcomes from randomised controlled trials with those from retrospective cohort studies 0.25	High, a low value favours nirmatrelvir and ritonavir
QALYs lost by patients who die	Estimated by derivation of discounted quality adjusted life expectancies for each of the modelled cohort based on the cohort's characteristics 6.44 QALYs for people aged ≥ 70, up to 15.57 for people aged ≥ 18 who are immunocompromised	High, a high value favours nirmatrelvir and ritonavir

Source: Based on observations from Table 21.

6.69 Table 19 summarises results of the base case analyses presented in the submission. The ICERs range from \$0 to < \$5,000 to \$15,000 to < \$25,000 per QALY gained for the four cohorts presented in the submission. A weighted ICER for the total population was calculated as scenario analysis (see Table 22).

Table 19: Results of the base case economic evaluations presented in the submission

	Nirmatrelvir and ritonavir	Placebo	Increment	ICER
Cohort: Aged ≥ 70				
Costs		\$759.93		¹
QALYS lost	0.0548	0.2012	0.1464	
Cohort: Aged ≥18 and immune-compromised*				
Costs		\$681.48		²
QALYS lost	0.1233	0.4750	0.3517	
Cohort: Aboriginal and Torres Strait Islander people aged ≥ 30 and ≥ 1 risk factor				
Costs		\$603.04		¹
QALYS lost	0.0715	0.2678	0.1964	
Cohort: Aged 50-69 & ≥ 1 risk factor				
Costs		\$474.68		³
QALYS lost	0.0293	0.0991	0.0698	

Source: Table 3.8.4 on p209 of the submission

QALY = quality adjusted life year

* assumed to include patients aged ≥ 18 previously requiring hospitalisation for COVID-19

The redacted values correspond to the following ranges:

¹ \$5,000 to < \$15,000

² \$0 to < \$5,000

³ \$15,000 to < \$25,000

- 6.70 The submission also presented cost-effectiveness analyses of molnupiravir versus placebo and of nirmatrelvir and ritonavir versus molnupiravir. As discussed in paragraphs 6.11 to 6.14, the meta-analyses that inform these comparisons are incomplete and, an indirect comparison of nirmatrelvir and ritonavir versus molnupiravir was not presented in the submission.
- 6.71 Table 20 summarises results of respecified base-case analyses that: (i) removes the treatment effect on the incidence of long COVID; (ii) reduces the baseline risk of death applied in the model; and (iii) applies a constant relative risk of 0.30 regardless of event (apart from long COVID). The incremental impact of each of these changes is shown for the cohort of patients aged ≥ 70 years. Table 20 also includes an estimate of cost-effectiveness for a cohort of patients aged 50 - 69 with ≥ 2 additional risk factors, consistent with the population that was reimbursed prior to the temporary expansion of the restriction to include patients aged 50 – 69 years with one additional risk factor (discussed at paragraph 2.12). As can be seen, the ICER when use of nirmatrelvir and ritonavir in patients aged 50 -69 with 1 additional risk factor is permitted is substantially higher than when the population is limited to patients with ≥ 2 additional risk factors (\$55,000 to < \$75,000/QALY compared with \$35,000 to < \$45,000/QALY). On this basis, the PBAC considered that the PBS restriction for patients aged 50 -69 years should revert to requiring at least 2 additional risk factors.
- 6.72 The ESC noted that, regardless of which set of results was considered, the ICERs for nirmatrelvir and ritonavir in patients aged 50-69 years were substantially higher than those calculated for the other patients groups (Table 19, Table 20).

Table 20: Results of the respecified economic evaluation conducted during the evaluation

	Nirmatrelvir and ritonavir	Placebo	Increment	ICER
Cohort: Aged ≥ 70				
Step 1: Removing treatment effect on long COVID				
Costs		\$759.93		¹
QALYS lost	0.0561	0.2012	0.1451	
Step 2: Step 1 and reducing baseline risk of mortality				
Costs		\$759.93		²
QALYS lost	0.0239	0.0724	0.0485	
Step 3: Step 2 and applying a constant RR of 0.3 for all events (respecified base case)				
Costs		\$759.93		²
QALYS lost	0.0271	0.0724	0.0453	
Cohort: Aged ≥18 and immune-compromised respecified base case *				
Costs		\$681.48		¹
QALYS lost	0.0545	0.1636	0.1092	
Cohort: Aboriginal and Torres Strait Islander people aged ≥ 30 and ≥ 1 risk factor respecified base case				
Costs		\$603.04		³
QALYS lost	0.0337	0.0945	0.0608	
Cohort: Aged 50-69 & ≥ 1 risk factor respecified base case				
Costs		\$474.68		⁴
QALYS lost	0.0168	0.0382	0.0214	
Cohort: Aged 50-69 & ≥ 2 risk factors respecified base case[^]				
Costs		\$528.17		⁵
QALYS lost	0.0220	0.0554	0.0334	

Source: Constructed during the evaluation

QALY = quality adjusted life year

* assumed to include patients aged ≥18 previously requiring hospitalisation for COVID-19

this cohort reflects the current PBS restrictions for patients aged 50-69 (which requires at least one additional risk factor)

[^] this cohort is a subset of the cohort of patients aged 50-69 & ≥ 1 risk, and reflects the PBS restrictions for patients aged 50-69 prior to the expansions recommended by PBAC in February and June 2023 (i.e. required at least two additional risk factors).

The redacted values correspond to the following ranges:

¹ \$5,000 to < \$15,000

² \$25,000 to < \$35,000

³ \$15,000 to < \$25,000

⁴ \$55,000 to < \$75,000

⁵ \$35,000 to < \$45,000

6.73 The results of key sensitivity analyses presented in the submission based on the cohort of patients aged ≥ 70 years are summarised in Table 21. This analysis is presented as an exemplar. The analyses for other cohorts are sensitive to the same variables. Additional sensitivity analyses conducted during the evaluation are shown. As can be seen, the results of the economic analyses are particularly sensitive to the estimated baseline risk of events (particularly death), the assumed reduction in risk of events (particularly death) associated with nirmatrelvir and ritonavir, and the assumed quality-adjusted life expectancy of patients who die in the acute phase of treatment.

Table 21: Results of key sensitivity analyses (using the cohort aged ≥ 70 as the exemplar) based on the submission's base case

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Base case for cohort aged ≥ 70		0.1464	1	
Baseline risk of hospitalisation (base case = 5%)				
• 2.5%		0.1463	1	↑
• 7.5%		0.1464	1	↓
Baseline risk of death (base case = 3%)				
• 1.5%		0.0739	2	↑
• 4.5%		0.2188	1	↓
RR of hospitalisation in patients treated with nirmatrelvir (base case = 0.41)				
• 0.21		0.1464	1	↓
• 0.62		0.1463	1	↑
RR of death in patients treated with nirmatrelvir (base case = 0.25)				
• 0.13		0.1695	1	↓
• 0.38		0.1212	1	↑
Same RR for hospitalisation, ICU and death (base case = 0.41 for hospitalisation, 0.37 for ICU care, 0.25 for mortality) ^a				
• 0.25 / 0.25 / 0.25		0.1464	1	↓
• 0.30 / 0.30 / 0.30		0.1367	1	↑
• 0.35 / 0.35 / 0.35		0.1271	1	↑
RR of long COVID in patients treated with nirmatrelvir (base case = 0.74) ^a				
• 1		0.1451	1	↑
Multivariate analysis varying baseline risk of death, RR of hospitalisation, RR of death, RR of long COVID ^a (base case = 3% / 0.41 / 0.25 / 0.74)				
• 3% / 0.15 / 0.15 / 1		0.1645	1	↓
• 1% / 0.5 / 0.5 / 1		0.0324	3	↑
QALYs lost in patients who die (base case = 6.440)				
• 3.22		0.0739	2	↑
• 9.66		0.2188	1	↓

Source: Table 3.9.2 on p197 of the submission and analyses conducted during the evaluation

a. analyses conducted during the evaluation

QALY = quality adjusted life year; RR = relative risk

The redacted values correspond to the following ranges:

¹ \$5,000 to < \$15,000

² \$15,000 to < \$25,000

³ \$35,000 to < \$45,000

6.74 The submission also presented scenario analyses as shown in Table 22. This included three scenarios reporting weighted ICERs for the overall population eligible for PBS subsidised nirmatrelvir and ritonavir, including one scenario representing the current PBS restrictions (Scenario #6) and additional scenarios to represent the population that was eligible prior to the extensions recommended in June 2023 and February 2023 (Scenario #7 and Scenario #8, respectively).

Table 22: Scenario analyses presented by the submission

Analysis	Parameters	Value	ICER
Collapsed indication #1 Aged 60+ no other risk criteria	Hospitalisation risk	3.5%	¹
	ICU admission risk	7.5%	
	Mortality risk	2.0%	
	PACS risk	10%	
	dQALE tariff	7.03	
Scenario #2 Aged 50-59 with 2 other risk factors	Hospitalisation risk	2.0%	²
	ICU admission risk	5.0%	
	Mortality risk	1.0%	
	PACS risk	10%	
	dQALE tariff	12.18	
Scenario #3 Aged 60-69 with 2 other risk factors	Hospitalisation risk	2.5%	¹
	ICU admission risk	5.0%	
	Mortality risk	1.5%	
	PACS risk	10.0%	
Scenario #4 Aged 50-59 with 1 other risk factors	Hospitalisation risk	1%	³
	ICU admission risk	5%	
	Mortality risk	0.5%	
	PACS risk	10%	
	dQALE tariff	12.18	
Scenario #5 Aged 60-69 with 1 other risk factors	Hospitalisation risk	2%	²
	ICU admission risk	5%	
	Mortality risk	1%	
	PACS risk	10%	
	dQALE tariff	10.65	
Scenario #6 Overall high-risk population currently eligible (50-59 1 RF and 60-69 1 RF)	Aged 70+	50%	¹
	Aged 18+ IC	15%	
	Aged 30+ ATSI HR1	5%	
	Aged 50-69 HR1	30%	
Scenario #7 Overall high-risk population prior to 1 July 2023 (50-59 2 RF and 60-69 1 RF)	Aged 70+	50%	¹
	Aged 18+ IC	15%	
	Aged 30+ ATSI HR1	5%	
	Aged 50+ HR2	15%	
	Aged 60+ HR1	15%	
Scenario #8 Overall high-risk population - criteria prior to 1 April and 1 July changes (50-59 2 RF and 60-69 2 RF)	Aged 70+	50%	¹
	Aged 18+ IC	15%	
	Aged 30+ ATSI HR1	5%	
	Aged 50-69 HR2	30%	

Source: Table 3.9.7 on p202 of the submission.

The redacted values correspond to the following ranges:

¹ \$5,000 to < \$15,000

² \$15,000 to < \$25,000

³ \$25,000 to < \$35,000

6.75 The PSCR acknowledged the variation in estimates of treatment effect across the various studies. Results of sensitivity analyses around the respecified analysis (i.e., with mortality rates set at 1% and no treatment effect on long COVID) but applying the point estimate (0.252), upper (0.768) and lower (0.083) confidence limits from a meta-analysis of the EPIC trials (Figure 4) are provided in the following table for the exemplar of patients aged ≥ 70 years. As can be seen, there are modest decreases in

the ICER if lower relative risks are applied but the ICER is very sensitive to increases in the assumed relative risks (indicating reduced treatment effect) associated with nirmatrelvir and ritonavir compared with placebo.

Table 23: Sensitivity analyses on treatment effect^a

	Incremental costs	Incremental QALYs	ICER
Cohort: Respecified base case for cohort aged ≥ 70 – RR = 0.30			
		0.0453	1
Point estimate of meta-analysis of RCTs (0.252)			
		0.0484	1
Lower confidence limit around point estimate from meta-analysis of RCTs (0.083)			
		0.0593	2
Upper confidence limit around point estimate from meta-analysis of RCTs (0.768)			
		0.0150	3

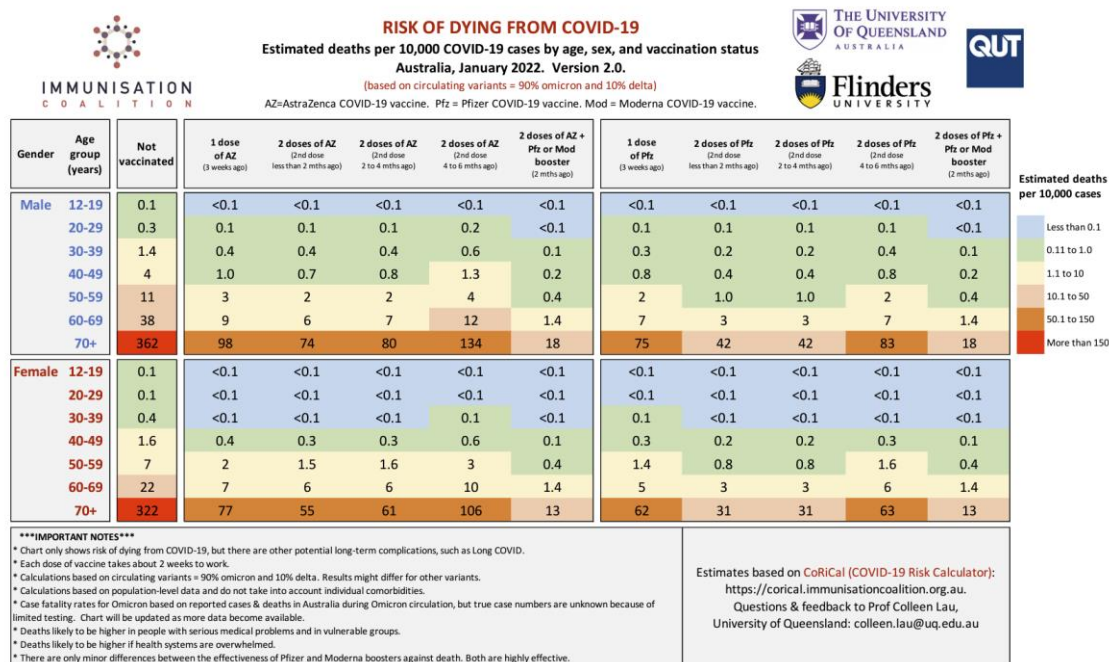
a. Meta-analysis (Figure 4) of EPIC-HR, EPIC-SR (mITT1): RR nirmatrelvir and ritonavir vs placebo (95% CI) 0.252 (0.083, 0.768), The redacted values correspond to the following ranges:

- ¹ \$25,000 to < \$35,000
- ² \$15,000 to < \$25,000
- ³ \$95,000 to < \$115,000

6.76 The ESC advised that baseline risks of death applied in the submission’s economic analysis appear to have been overestimated and had poor face validity.

6.77 The ESC noted the COVID-19 mortality estimates from CoRiCal (COVID-19 Risk Calculator) are shown in Figure 9, and considered the estimates in the submission in the context of the CORiCal estimates (Figure 9).

Figure 9: COVID-19 mortality estimates from CoRiCal (COVID-19 Risk Calculator)



6.78 The ESC advised that a more appropriate base case may be as conducted during the evaluation with respect to baseline mortality risks, and no treatment effect on long

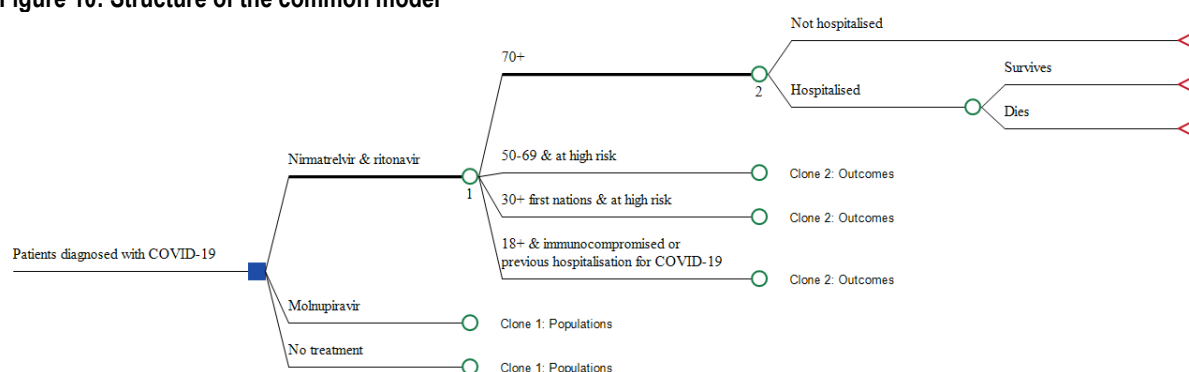
COVID. Further, the ESC noted that the sensitivity analyses applying pooled estimates of treatment effects from a meta-analysis of RCTs were informative (Table 23).

- 6.79 The ESC advised it was not appropriate to use observational studies to derive differential estimates of treatment effect to be applied in the economic analysis.
- 6.80 The pre-PBAC response applied the costs of a longer telehealth consultation lasting at least 6 minutes (MBS item 91891 Fee \$41.20) to the respecified base case. The analysis showed that the model was not highly sensitive to the increase in MBS costs (ICER increase of \$0 to < \$5,000, \$0 to < \$5,000, \$0 to < \$5,000, \$0 to < \$5,000 for ≥ 18 immunocompromised, ≥ 30 ATSI, ≥70 and 50-69 with at least 2 risk factors, respectively) even when this cost is conservatively applied for all patients (results not verified).
- 6.81 The pre-PBAC response noted the respecified base case conducted during the evaluation included a 66% reduction in the baseline mortality rate and stated that a 50% reduction in the baseline mortality rate would be a more reasonable assumption.
- 6.82 The response offered a revised price of AEMP \$ [REDACTED]. At this price, applying a flat relative risk of 0.3 for hospitalisation, no treatment effect for long COVID and a 50% reduction in baseline mortality, Paxlovid is highly cost-effective in all four subgroups, with ICERs of \$5,000 to < \$15,000/QALY, \$5,000 to < \$15,000/QALY, \$5,000 to < \$15,000/QALY and \$15,000 to < \$25,000/QALY for people aged 70+, 18+ moderately or severely immunocompromised, 30+ ATSI with at least one additional risk factor and people 50-69 with at least two additional risk factors, respectively. Based on subgroup weightings of 50%, 15%, 5% and 30%, respectively, the weighted ICER for the overall population is estimated to be \$5,000 to < \$15,000/QALY (results not verified).

Revised economic analysis

- 6.83 At the request of the ESC, a simplified revised model focussed on the key drivers of cost-effectiveness of the antivirals used to treat COVID-19 was developed. The simplified model allows both of the antiviral products to be assessed under the same conditions. The specifications of the common model are provided below in sufficient detail to allow the results to be reproduced by the sponsor.
- 6.84 The structure of the common model is shown in Figure 10. The common model does not include any impact of long COVID on patients. The only outcome captured by this model is QALYs gained by averting deaths due to COVID-19. The only costs included in this economic evaluation are drug treatment costs and hospitalisation costs.

Figure 10: Structure of the common model



6.85 The key inputs applied in the sponsor’s model and the common model are summarised in Table 24. The inputs applied in the common model reflect ESC advice regarding the most appropriate estimates, that were supported based on review of the inputs provided in the sponsor submissions and evaluations for both OAVs. An alternative set of inputs is also presented as a sensitivity analysis.

Table 24: Comparison of key inputs applied in the common model with those applied in the submission’s model

Parameter	Common model	Nirmatrelvir & ritonavir submission
Baseline risk of hospitalisation		
70+	5%	5%
50-69 with ≥ 2 risk factors	2%	2%
50-69 with ≥ 1 risk factor	1.5%	1.5%
First Nations	3%	3%
18+ and immune compromised	4%	4%
Proportion of hospitalised patients requiring admission to ICU		
70+	10%	10%
50-69 with ≥ 2 risk factors	5%	5%
50-69 with ≥ 1 risk factor	5%	5%
First Nations	10%	10%
18+ and immune compromised	10%	10%
Baseline risk of death in the acute phase following COVID-19		
70+	1% [@]	3%
50-69 with ≥ 2 risk factors	0.33% [@]	1%
50-69 with ≥ 1 risk factor	0.25% [@]	0.75%
First Nations	0.67% [@]	2%
18+ and immune compromised	1% [@]	3%
Treatment effect (odds ratio) for nirmatrelvir and ritonavir		
70+	0.283 [#]	0.41 for hospitalisations, 0.37 for ICU admissions, 0.25 for death
50-69 with ≥ 2 risk factors	0.283 [#]	
50-69 with ≥ 1 risk factor	0.283 [#]	
First Nations	0.283 [#]	
18+ and immune compromised	0.283 [#]	
Discounted QALYs lost by a patient who dies due to COVID-19		
70+	6.44	6.44
50-69 with ≥ 2 risk factors	12.18	12.18

Parameter	Common model	Nirmatrelvir & ritonavir submission
50-69 with ≥ 1 risk factor	12.18	12.18
First Nations	13.00	13.00
18+ and immune compromised	15.57	15.57
Cost of hospitalisation		
General ward	\$6,419	\$6,419
ICU	\$20,675	\$20,675

@ The COVID Risk Calculator chart, produced by the Immunisation Coalition (Australia), that estimated the risk of death from COVID-19 based on age, sex, and vaccination status (with 90% Omicron/10% Delta variants circulating) is provided to give some context to the estimates applied in the common model.

Based on outcomes from the high-risk subgroup in the EPIC-SR trial

6.86 The results generated by the common model are presented below, including the estimated ICERs for each of the cohorts that correspond to one of the Streamlined Authority Required restrictions, applying the same key parameters as deemed reasonable during the evaluation.

Table 25: Results of the respecified economic evaluation conducted during the evaluation – nirmatrelvir and ritonavir

	Nirmatrelvir and ritonavir	Placebo	Increment	ICER per QALY
Cohort: Aged ≥ 70				
Costs		\$392.23		¹
QALYS lost	-0.0189	-0.0644	0.0455	
Cohort: Aged ≥18 and immune-compromised				
Costs		\$313.78		²
QALYS lost	-0.0454	-0.1557	0.1103	
Cohort: Aboriginal and Torres Strait Islander people aged ≥ 30 and ≥ 1 risk factor				
Costs		\$235.34		³
QALYS lost	-0.0251	-0.0867	0.0616	
Cohort: Aged 50-69 & ≥ 1 risk factor				
Costs		\$106.98		⁴
QALYS lost	-0.0087	-0.0305	0.0217	
Cohort: Aged 50-69 & ≥ 2 risk factors				
Costs		\$142.64		⁵
QALYS lost	-0.0117	-0.0406	0.0289	
Current Scenario^a – Overall ICER with current nirmatrelvir and ritonavir restrictions and proportions based on utilisation^c				
Costs		\$303.46		¹
QALYS lost	-0.0203	-0.0695	0.0492	
2RF Scenario^a – Overall ICER with requirement for ≥ 2 risk factors for cohort aged 50-69, all other settings same as current scenario				
Costs		\$310.47		¹
QALYS lost	-0.0208	-0.0715	0.0506	
Pre-PBAC response scenario – Overall ICER with requirement for ≥ 2 risk factors for cohort aged 50-69, and price from pre-PBAC response (DPMQ = \$1,251.34; AEMP=\$1,130), all other settings same as current scenario				
Costs		\$310.47		³
QALYS lost	-0.0208	-0.0715	0.0506	
Revised scenario with price reduction^b–Overall ICER with price reduction corresponding to PBAC advice (ICER ≤\$15,000/QALY in all subgroups and requirement for ≥ 2 risk factors for cohort aged 50-69)				
Costs		\$310.47		²
QALYS lost	-0.0208	-0.0715	0.0506	

a. The price of nirmatrelvir and ritonavir applied is the requested DPMQ in the submission, based on an ex-manufacturer price of \$█ per pack.

b. The nirmatrelvir and ritonavir weighted DPMQ in the revised scenario is \$ [redacted] ([redacted]% reduction from the proposed DPMQ in pre-PBAC response of \$ [redacted] (based on AEMP of \$ [redacted]), and [redacted]% from the current DPMQ of \$1,114.84). The effective DPMQ for each individual subgroup is shown in Table 26.

c. The proportions applied in this analysis are 70+ = 55%; 50-69 with risk factors =20%; 30+ First Nations with risk factors =16%; 18+ immunocompromised or previously hospitalised for COVID-19 =9%, shown in Table 26.

The redacted values correspond to the following ranges:

¹\$25,000 to < \$35,000

²\$5,000 to < \$15,000

³\$15,000 to < \$25,000

⁴\$55,000 to < \$75,000

⁵\$45,000 to < \$55,000

6.87 The revised scenario in Table 25 corresponds to PBAC advice that the ICER should be no greater than \$15,000/QALY in any subgroup. The effective DPMQ corresponding to this ICER threshold in each individual subgroup is shown in Table 26, as well as the assumed distribution of patients across populations used for calculation of the weighted effective DPMQ. The PBAC noted the price that was offered in the pre-PBAC response reduced the estimated weighted ICER as shown in Table 25, however considered that a further price reduction was required to achieve cost-effectiveness based on plausible inputs.

Table 26: Effective DPMQ of nirmatrelvir and ritonavir required for each individual population to achieve ICER of <\$15,000/QALY

	Weighted effective DPMQ	Effective DPMQ in 70+ population	Effective DPMQ in 50-69 +RF	Effective DPMQ in First Nations	Effective DPMQ in 18+ immune compromised
Proportions ^a	n/a	55.1%	19.6%	16.4%	8.9%
Effective DPMQ (\$)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] ^b

a. As observed in prescribing of oral antivirals the 6 months ending 24 Sep 2023, shown rounded to one decimal place.

b. Proposed DPMQ generates an ICER in this population below the target ICER (DPMQ=\$ [redacted])

6.88 The PBAC noted the limitations of the evidence base available to inform the treatment effect assumed to be associated with nirmatrelvir and ritonavir in the economic model (Table 10), and uncertainties associated with estimation of future benefits of treatment which could vary according to future population characteristics such as vaccination rate, and based on disease characteristics such as virulence of SARS-CoV-2 variants. The PBAC also noted the objection in the pre-PBAC response to the extent of reduction in mortality rates applied in the revised economic analysis (see paragraph 6.81).

6.89 A multivariate sensitivity analysis was conducted and the results are presented in Table 27 to explore these uncertainties. This analysis applies assumptions that are more favourable to the intervention than were applied in the evaluation common model shown in Table 24, as follows:

- Odds ratio (OR) is the result obtained by meta-analysis of results from the original high-risk trial and from the high-risk subgroups of the more contemporary trials i.e., for nirmatrelvir and ritonavir, OR = 0.166 (see Figure 7).
- Baseline risks of death are one-half (rather than one-third) of those applied in the submission’s model and are thus 1.5%, 0.5%, 1.0%, and 1.5% for the 70+, 50-69

with two risk factors, First Nations with risk factors, and 18+ immunocompromised or previously hospitalised for COVID-19 populations, respectively.

6.90 The PBAC’s advice in relation to the MSA is provided in paragraph 7.18.

Table 27: Results of the alternative economic evaluation – nirmatrelvir and ritonavir (multivariate sensitivity analysis)

	Nirmatrelvir and ritonavir	Placebo	Increment	ICER
Cohort: Aged ≥ 70				
Costs		\$392.23		¹
QALYS lost	-0.0167	-0.0966	0.0799	
Cohort: Aged ≥18 and immune-compromised				
Costs		\$313.78		¹
QALYS lost	-0.0401	-0.2336	0.1934	
Cohort: Aboriginal and Torres Strait Islander people aged ≥ 30 and ≥ 1 risk factor				
Costs		\$235.34		¹
QALYS lost	-0.0221	-0.1300	0.1079	
Cohort: Aged 50-69 & ≥ 2 risk factors				
Costs		\$142.64		²
QALYS lost	-0.0103	-0.0609	0.0506	
MSA 2RF Scenario^a – Overall ICER with requirement for ≥ 2 risk factors for cohort aged 50-69, all other settings same as current scenario				
Costs		\$11,197.23		¹
QALYS lost	-0.0184	-0.1072	0.0888	
MSA Revised Scenario with price reduction^b–Overall ICER with price reduction corresponding to PBAC advice (ICER ≤\$15,000/QALY in all subgroups and requirement for ≥ 2 risk factors for cohort aged 50-69)				
Costs		\$310.47		¹
QALYS lost	-0.0184	-0.1072	0.0888	

a The price of nirmatrelvir and ritonavir applied is the requested DPMQ in the pre-PBAC response, of \$ (based on AEMP of).

b The nirmatrelvir and ritonavir weighted DPMQ in the revised scenario is \$ (% reduction from the proposed DPMQ in pre-PBAC response of \$ (based on AEMP of).

c. The proportions applied in this analysis are 70+= 55%; 50-69 with risk factors =20%; 30+ First Nations with risk factors =16%; 18+ immunocompromised or previously hospitalised for COVID-19 =9%, shown in Table 26.

The redacted values correspond to the following ranges:

¹ \$5,000 to < \$15,000

² \$15,000 to < \$25,000

Drug cost/patient/course

6.91 The proposed dispensed price per course of treatment with nirmatrelvir and ritonavir is \$| based on the price proposed in the pre-PBAC response.

Estimated PBS usage & financial implications

6.92 This submission was considered by DUSC.

6.93 The submission used an epidemiological approach to estimate utilisation of nirmatrelvir and ritonavir and the associated financial implications for the PBS. As noted by the submission, any set of estimates of PBS expenditure into the future will be associated with a high level of uncertainty due to the unknown characteristics of future COVID-19 variants e.g., transmissibility, severity of symptoms and risk of hospitalisation.

6.94 The steps taken and the sources of data used in deriving estimates of use of nirmatrelvir and ritonavir were:

- Estimation of total number of cases of COVID-19 in Australia: estimated by applying rates per 100,000 population by age group for the wave experienced between 15 December 2021 - 7 May 2023 (as reported in COVID-19 Australia report, Epidemiology Report 74) to the ABS population (3222.0 Series B) estimates of persons by age.
- Estimation of proportion of patients with COVID-19 at increased risk of severe disease (to estimate patients eligible for treatment under the PBS) were based on:
 - MacIntyre et al, 2018, who estimated the proportion of patients aged 18-49 who were immunosuppressed; MacIntyre 2018 estimated the immunosuppressed populations based on estimates of the populations living with cancer, HIV, organ transplants, respiratory syndromes such as asthma and chronic obstructive pulmonary disease, dialysis and autoimmune diseases and divided these populations into two immunosuppression categories. Severe immunosuppression was defined as a condition in which quantifiable data existed to demonstrate a risk for infection more than twice that of an immunocompetent person. Immunosuppressed persons were considered to have no residual immunity from vaccination. The PBS restriction for persons aged ≥ 18 years with immunosuppression includes several other conditions that are associated with immunosuppression. The evaluation considered that the method adopted potentially underestimated the amount of immunosuppression in the population; and
- Clark et al, 2020 who estimated the proportion of the population with one identified risk condition (for COVID-19) across Oceania in people aged ≥ 50 years.
- Estimation of uptake of oral antivirals in the eligible population: estimated based on PBS services for nirmatrelvir and ritonavir and for molnupiravir.
- Estimation of market share for nirmatrelvir and ritonavir: estimated based on PBS data and sponsor's anticipations of market share into the future given the extensions to the restrictions for nirmatrelvir and ritonavir but not molnupiravir. The submission presented a survey of 400 GPs conducted by IQVIA. The submission claimed the sample was representative of 35,000 GPs in Australia. The majority (60%) of GPs surveyed appear to have been aware of recent changes to the PBS eligibility criteria for COVID-19 antiviral treatments including extension of eligibility criteria for nirmatrelvir and ritonavir however, as shown in Figure 11, the PBS data have not indicated any corresponding meaningful change to the market share of nirmatrelvir and ritonavir. The evaluation considered it was likely that the submission's estimates of market share into the future are overestimates.

6.95 The key inputs to the calculation of estimates of number of patients to be prescribed nirmatrelvir and ritonavir are summarised in Table 28.

Table 28: Data sources and parameter values applied in the utilisation and financial estimates

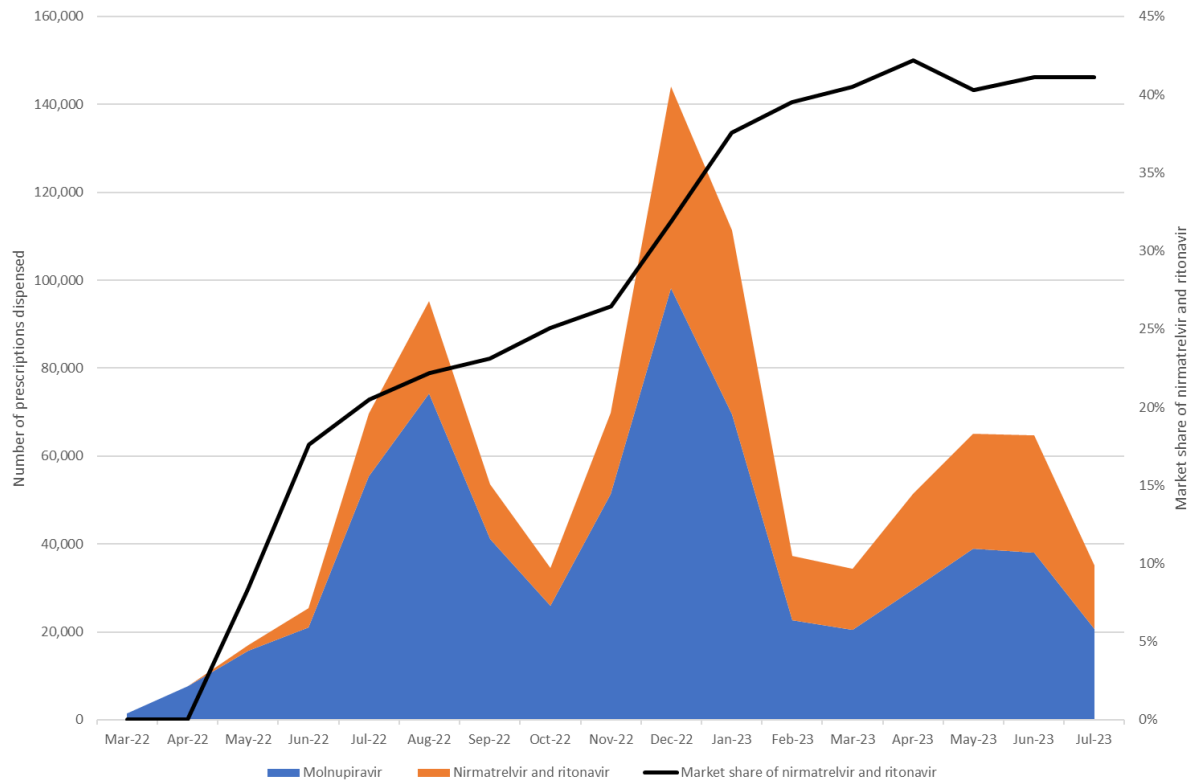
Parameter	Value applied and source	Commentary on the submission	DUSC comments
Adult Australian population	Source: ABS Series B projections		
Estimated number of cases of COVID-19 in the Adult population	Source: COVID-19 Australia report, Epidemiology Report 74 COVID-19 cases per 100,000 people (15 Dec 2021 - 7 May 2023) 18-29 53,895.70 30-39 51,034.4 40-49 48,575.8 50-59 40,200.0 60-69 31,595.3 70-79 25,582.6 80-89 26,445.6 90+ 37,373.3	The application of estimates from 2022 – mid 2023 introduces uncertainty in estimates as the past may not be a reliable predictor of the future.	DUSC considered this may be overestimated. DUSC considered it would be unlikely for approximately 25%-50% of the Australian population to be infected with COVID-19 annually. DUSC considered whether influenza modelling could be used.
Proportion of patients at increased risk of progression to severe COVID	Source: Age grp Proportion MacIntyre 2018: 18-49: 3.76% Clark 2020: 50-54: 26% 55-59: 32% 60-64: 35% 65-69: 38% 70-100: 100%	The application of estimates of the proportion of patients in the 18-49 year population with severe immunosuppressive conditions from MacIntyre 2018 appears appropriate as does the application of proportion of the population with risk factors as reported by Clark 2020	DUSC noted the population risk factors for severe COVID-19 were determined early in the pandemic and there may be differences over time.
Uptake of antivirals	Source: assumptions based on comparison of the estimated number of patients with COVID-19 using an epidemiological approach and the number of oral antiviral PBS prescriptions dispensed from 1 May 2022 to 30 April 2023 and adjustment for extensions to the PBS restrictions for nirmatrelvir and ritonavir after April 2023. Age group: Uptake 18-49: 35% 50-59: 40% 60-69: 43% 70+: 45%	The submission's uptake assumptions were constant throughout the six year period of the estimates, and acknowledged difficulty in estimating the later years due to a high degree of uncertainty regarding the characteristics of future COVID-19 variants such as transmissibility, severity of symptoms and risk of hospitalisation.	DUSC considered the treatment uptake rate assumptions to be reasonable as they were consistent with existing PBS utilisation. DUSC noted the closure of COVID-19 care clinics and the reduction in community testing.

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Parameter	Value applied and source	Commentary on the submission	DUSC comments
Market share of nirmatrelvir and ritonavir	<p>Source: Estimation of market share based on PBS data and sponsor's assumptions. The submission assumed that 20% of the eligible population are contraindicated or otherwise unsuitable for treatment with nirmatrelvir and ritonavir and would be suitable for treatment with molnupiravir. The submission also presented a survey of 400 GPs.</p> <p>Assumptions:</p> <p>2023: █████% (average YTD)</p> <p>2024: █████%</p> <p>2025: █████%</p> <p>2026: █████%</p> <p>2027: █████%</p> <p>2028: █████%</p> <p>2029: █████%</p>	<p>Likely overestimated, particularly beyond 2026. The market share of nirmatrelvir and ritonavir appears to have stabilised at approximately 40%. It is possible that, given the time pressures faced by prescribers, they may prescribe molnupiravir when a patient is on any therapy that could potentially interact with nirmatrelvir and ritonavir even though it may be theoretically possible to manage the potential for an interaction.</p>	<p>DUSC considered the market share would likely increase as clinicians become more familiar with managing drug-drug interactions and noted increased utilisation in jurisdictions where programs were implemented to support nirmatrelvir and ritonavir utilisation.</p>
Cost of antivirals	<p>The cost applied for nirmatrelvir and ritonavir was the requested DPMQ of \$████. The cost applied for molnupiravir was the DPMQ at the time of submission which was \$1,102.24 (July 2023).</p>	<p>The submission assumed that the price of nirmatrelvir and ritonavir was █████% higher than the cost of molnupiravir. The submission assumed cost offsets from increased rates of substitution of molnupiravir with nirmatrelvir and ritonavir, therefore the difference between prices of the treatments had a significant impact on the net costs estimated by the submission.</p>	

Source: Table 4.13 on pp217-218 of the submission and DUSC Advice Table 5.

Figure 11: Total prescriptions dispensed for nirmatrelvir and ritonavir and for molnupiravir by month



Source: PBS data from 1 Mar 2022 to 31 July 2023

6.96 Based on an assumption of one prescription per patient, the submission’s estimates of the number of units of nirmatrelvir and ritonavir that will be dispensed from 2024 to 2029 are summarised in Table 29. To put the estimates in Table 29 into context, the number of units of both antiviral products (nirmatrelvir and ritonavir; and molnupiravir) dispensed in the year ending 31 July 2023 was 700,000 to < 800,000 and market share of nirmatrelvir and ritonavir has been relatively stable at approximately 42% since February 2023. If market share was stable over a year, this would equate to approximately 300,000 to < 400,000 prescriptions for nirmatrelvir and ritonavir.

Table 29: Estimated use and financial implications

	2024	2025	2026	2027	2028	2029
Estimated extent of use – assuming continuation of current restrictions						
Estimated number of patients eligible to be prescribed an oral antiviral on the PBS	1	1	1	1	1	1
Total number of prescriptions for antivirals dispensed*	2	2	2	3	3	3
Number of prescriptions dispensed for nirmatrelvir and ritonavir ^a	4	5	6	7	7	7
Estimated financial implications of nirmatrelvir and ritonavir						
Cost to PBS/RPBS less co-payments	8	9	10	11	11	11
Estimated financial implications for molnupiravir						
Cost to PBS/RPBS less co-payments	12	12	12	12	12	12
Net financial implications						
Net cost to PBS/RPBS	13	13	14	8	8	8
Net cost to MBS	15	15	15	15	15	15
Net cost to PBS/RPBS/MBS	13	13	14	8	8	8
Pre-PBAC response – revised estimates assuming the restrictions applying prior to the temporary expansion (require at least 2 additional risk factors for the 50-69 age-group)						
Total number of prescriptions for antivirals dispensed	6	7	7	7	7	7
Nirmatrelvir and ritonavir market share	%	%	%	%	%	%
Number of prescriptions dispensed for nirmatrelvir and ritonavir	16	4	5	6	6	6
Reduction in prescriptions dispensed for nirmatrelvir and ritonavir, compared with submission	23%	23%	23%	22%	22%	22%

* Back-calculated during the submission by application of market share of nirmatrelvir and ritonavir (as projected in Table 28)

Sources: Table 4.213 on p226 Table 4.3.2 on p227, Table 4.4.1 on p228, Tables 4.5.2 and 4.5.3 on p230 of the submission), and pre-PBAC response.

^a Assuming one prescription per patient per year as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 1,000,000 to < 2,000,000

² 700,000 to < 800,000

³ 800,000 to < 900,000

⁴ 300,000 to < 400,000

⁵ 400,000 to < 500,000

⁶ 500,000 to < 600,000

⁷ 600,000 to < 700,000

⁸ \$600 million to < \$700 million

⁹ \$700 million to < \$800 million

¹⁰ \$800 million to < \$900 million

¹¹ > \$1 billion

¹² Net cost saving

¹³ \$400 million to < \$500 million

¹⁴ \$500 million to < \$600 million

¹⁵ \$0 to < \$10 million

¹⁶ 200,000 to < 300,000

- 6.97 The total cost to the PBS/RPBS of continued listing of nirmatrelvir and ritonavir was estimated to be >\$1 billion in Year 6, and a total of >\$1 billion in the first 6 years of listing based on assumptions of continued prescribing of antivirals for COVID-19 at the rates observed over the past year, with some additional use due to an assumption of continuation of the current PBS restrictions for nirmatrelvir and ritonavir. The net cost in Year 6 is estimated to be \$600 million to < \$700 million in Year 6 due to offsets from increased rates of substitution of molnupiravir with nirmatrelvir and ritonavir.
- 6.98 Any set of estimates of PBS expenditure into the future for treatments for COVID-19 will be associated with a high level of uncertainty due to the unknown characteristics of future COVID-19 variants e.g., transmissibility, severity of symptoms and risk of hospitalisation and due to unpredictable developments such as availability of new treatments and vaccines. However, the submission's estimates of use of nirmatrelvir and ritonavir are likely overestimates given the assumption of a doubling of the market share of nirmatrelvir and ritonavir by 2027.
- 6.99 The sensitivity analyses presented by the submission indicated a high level of uncertainty, with annual net costs to the PBS/RPBS for nirmatrelvir and ritonavir, ranging between \$200 million to < \$300 million and >\$1 billion for Year 6 estimates compared with \$600 million to < \$700 million in the submission's base case (Submission Table 4.6.2).
- 6.100 An additional sensitivity analysis conducted during the evaluation (Table 30) shows that the financial implications are sensitive to variations in the market share assumed to be taken by nirmatrelvir and ritonavir. The Year 6 net cost to the PBS/RPBS for nirmatrelvir and ritonavir was estimated to be \$100 million to < \$200 million in a sensitivity analysis that assumed there was no change to market share of nirmatrelvir and ritonavir, compared with \$600 million to < \$700 million estimated in the submission's base case.

Table 30: Sensitivity analysis assuming no change to market share of nirmatrelvir and ritonavir*

	2024	2025	2026	2027	2028	2029
Cost of nirmatrelvir and ritonavir to PBS/RPBS less co-payments	¹	²	²	²	²	²
Cost offsets due to reduced use of molnupiravir	- ³	- ³	- ³	- ³	- ³	- ³
Net cost to PBS/RPBS	⁴	⁵	⁶	⁶	⁶	⁶

* Conducted during the evaluation.

The redacted values correspond to the following ranges:

¹ \$400 million to < \$500 million

² \$500 million to < \$600 million

³ Net cost saving

⁴ \$300 million to < \$400 million

⁵ \$200 million to < \$300 million

⁶ \$100 million to < \$200 million

6.101 The DUSC noted that the financial analyses assumed similar rates of COVID-19 and similar rates of use of antivirals for COVID-19 as has occurred in the past. The DUSC considered that this is unlikely to occur and that the number of COVID-19 cases estimated by the submission was likely overestimated. The DUSC considered whether modelling based on influenza rather than modelling based on COVID-19 case numbers during pandemic dominated years could be used to predict future cases of COVID-19. The DUSC noted the global pattern of ‘skip-and-resurgence behaviour’ of influenza where an outbreak ‘skipped’ countries, follow by a ‘resurgence’ of an outbreak occurring in the following year. Over time, each successive outbreak would expose the population further to a particular strain, building population immunity to that strain. Therefore, the susceptible pool of individuals available for infection may reduce below a threshold level and as such, an outbreak is less likely to occur until there is a shift in the circulating virus strain.¹⁸

6.102 The DUSC considered that market share of nirmatrelvir and ritonavir would likely increase over time as clinicians become more familiar with managing drug-drug interactions and noted increased utilisation in jurisdictions where programs were implemented to support nirmatrelvir and ritonavir utilisation (e.g. Quality Use of Medicines program was implemented in South Australia that has encouraged higher use of NIR/r rather than molnupiravir).

6.103 The pre-PBAC response stated that seasonality has not yet been observed with COVID-19 infections globally, other than simple increases in absolute patient numbers during colder periods. With the return of extensive international travel and an ability of the virus to infect more easily than influenza, basing expected case numbers on influenza trends may underestimate the likely incidence of COVID-19 infections. Reduced

¹⁸ He, D., Lui, R., Wang, L. et al. Global Spatio-temporal Patterns of Influenza in the Post-pandemic Era. Sci Rep 5, 11013 (2015). <https://doi.org/10.1038/srep11013>

testing and reporting of COVID-19 infections were noted as additional challenges with respect to the estimates.

Quality Use of Medicines

- 6.104 The submission reported that the sponsor has been working to support clinicians managing drug-drug interactions with nirmatrelvir and ritonavir since its listing on the PBS.
- 6.105 The submission requested that the Prescriber bag listing for Paxlovid remain on the PBS to address the issue of patients presenting too late for treatment. From 1 November 2022 to 30 April 2023, 9,457 Prescriber Bag supplies were dispensed for molnupiravir and 9,898 prescriber bag prescriptions were dispensed for nirmatrelvir and ritonavir.
- 6.106 The submission also reported that the sponsor supported the pharmacy prescribing of nirmatrelvir and ritonavir and also pre-emptive or advanced prescribing of nirmatrelvir and ritonavir.
- 6.107 The recommended dosage is 300 mg nirmatrelvir (administered as two 150 mg tablets) with 100 mg ritonavir (administered as a single 100 mg tablet) with all three tablets taken together orally twice daily for 5 days, which corresponds to the requested maximum quantity of one pack. For patients with moderate renal impairment, a reduced dose of 150 mg nirmatrelvir (administered as one 150 mg tablets) with 100 mg ritonavir (administered as a single 100 mg tablet) is recommended to be taken twice daily for 5 days. Nirmatrelvir and ritonavir is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73m²). The TGA-approved product information describes two pack configurations, one for patients with no dose adjustment and a second for patients with moderate renal impairment, however the submission is not proposing listing of the pack for patients with moderate renal impairment, which may be a Quality Use of Medicines issue. The TGA-approved product information states that patients with moderate renal impairment should be alerted “that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours”, which means that five nirmatrelvir tablets would remain unused at the end of the course.

Financial Management – Risk Sharing Arrangements

- 6.108 The submission does not express any willingness to enter into any risk sharing arrangement nor any price-volume agreement.
- 6.109 The pre-PBAC response stated that it is inherently difficult to predict the trajectory of the pandemic, including evolution of the COVID-19 virus, the emergence of new variants and the need for and use of antivirals to treat patients at risk of severe disease. The pre-PBAC response stated that a risk sharing arrangement intended to cap expenditure/utilisation is not appropriate in this instance.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC provided advice regarding nirmatrelvir and ritonavir (Paxlovid), for the treatment of patients with mild to moderate Coronavirus disease (COVID-19) who are at high risk of severe disease requiring hospitalisation. The PBAC maintained its previous advice that nirmatrelvir and ritonavir is preferred over molnupiravir in a scenario where both oral antivirals are able to be used based on clinical evidence showing greater efficacy with nirmatrelvir and ritonavir. The PBAC recommended that, at its current price, there should be a change to the restriction for patients aged 50-69 years, which currently allows access for patients with one or more additional risk factors, to revert to the requirement for two or more risk factors, due to reduced cost-effectiveness in this lower risk population. The PBAC noted that a price reduction was offered in the pre-PBAC response however the proposed price remained higher than the current price. The PBAC advised that a price reduction is required from the current price because cost-effectiveness has almost certainly declined since the initial decision to recommend listing on the PBS was made.
- 7.2 The PBAC noted the input received from individuals and organisations which supported the ongoing listing of nirmatrelvir and ritonavir and described a range of benefits of treatment including potential to reduce symptoms and prevent severe COVID.
- 7.3 The PBAC advised that an Authority Required (STREAMLINED) restriction level remained appropriate.
- 7.4 The PBAC advised that the Prescriber Bag listing should be maintained for nirmatrelvir and ritonavir for patients requiring urgent treatment as described in the submission (see paragraph 1.3).
- 7.5 The PBAC noted the submission's request to retain the PBS restrictions currently in place for nirmatrelvir and ritonavir, and the clarification provided in the pre-PBAC response that acknowledged that amendments of the restriction for nirmatrelvir and ritonavir for patients aged 50-69 were intended to apply only until the Commonwealth purchased stock was exhausted or had expired. The PBAC recommended that the restriction for nirmatrelvir and ritonavir be amended to revert to the February 2023 restrictions corresponding to high risk, i.e. revert to requiring at least 2 additional risk factors for the 50-69 age-group. The PBAC considered that this change would be required to support continued listing.
- 7.6 The PBAC noted the submission's request to remove the caution from the PBS restriction (see paragraphs 3.5 to 3.7). The PBAC noted that nirmatrelvir and ritonavir is prescribed under Section 85 for the general community. In contrast, ritonavir as a single agent is listed under Section 100 as a highly specialised drug, managed by prescribers who are familiar with the medicine and its interactions. The PBAC recommended the caution regarding drug-drug interactions should be retained in the listing due to the risk of serious adverse reactions due to interactions with other

medicines as documented in the TGA-approved PI.

- 7.7 The PBAC noted that timely access to OAV, including PBS listing to facilitate distribution through community pharmacy, had been an important component of Australia's pandemic response, based on the best evidence available in early 2022 (see paragraphs 2.7 to 2.10).
- 7.8 The PBAC noted that based on the clinical evidence reviewed, nirmatrelvir and ritonavir appeared to be more effective treatment than molnupiravir (Table 11), however nirmatrelvir and ritonavir is contra-indicated in patients with severe renal or hepatic impairment, and contraindicated for use with certain other drugs, due to the risk of significant drug-drug interactions. The PBAC noted that these contraindications are clinically important for some vulnerable patients and must be managed carefully by prescribers.
- 7.9 The PBAC noted there was significant variation in the estimates of treatment effect reported by the randomised trials and observational studies (Table 11). The PBAC noted that the observational trials were subject to a range of biases. Although RCTs are of a higher quality, observational studies may be more representative of effectiveness in practice. The PBAC noted that estimates of treatment effect (in terms of incidence of hospitalisation or death) from EPIC-SR (including the high risk subgroup) and some of the observational studies did not reach statistical significance. The PBAC considered that, overall, the treatment effect of nirmatrelvir and ritonavir in practice appeared to be less than what was expected at the time it was recommended for inclusion on the PBS based on the results of EPIC-HR (see paragraph 6.25). The PBAC noted that the nirmatrelvir and ritonavir arm of the PANORAMIC trial is ongoing, and results have not yet been reported (paragraph 6.8).
- 7.10 The PBAC noted that the submission applied relative risks from published meta-analyses in the economic analyses. The published meta-analyses were incomplete in that they did not include all studies identified by the submission as being relevant. Furthermore, the meta-analyses included studies that did not satisfy the submission's inclusion/exclusion criteria for presentation in the submission (paragraph 6.12).
- 7.11 The PBAC noted that the pre-PBAC response had proposed a lower price than the submission, however the proposed ex-manufacturer price (\$| per pack) remained higher than the current price for nirmatrelvir and ritonavir (\$1,000 per pack). The PBAC considered that the current price is the absolute maximum and, reflecting the post-pandemic evolution of the disease, the price should be lower than proposed in the pre-PBAC response, and not higher than the current price.
- 7.12 The PBAC noted the large patient population that was forecast by the sponsor, of approximately 500,000 to < 600,000 to 600,000 to < 700,000 patients to be treated with OAV per year in the base case (Table 29; pre-PBAC response estimates). The PBAC noted the significant budget impact that was estimated by the sponsor, and considered the opportunity cost associated with the proposed continuation of the PBS listing at the proposed price. The PBAC considered that in this situation, it was

appropriate and necessary that the ICER that would define acceptable cost-effectiveness should be no greater than \$15,000/QALY in any of the patient subgroups.

- 7.13 The PBAC noted that the ICER for the 70+ cohort was similar to the overall weighted ICER (generated by weighting costs and weighting benefits, before calculating the ratio), however there was a wide range between the estimated ICERs for the subgroups shown in Table 25. Given the limitations of the data available (see paragraph 6.88), the PBAC advised that it was not appropriate to value nirmatrelvir and ritonavir based on the overall weighted ICER, and instead the cost-effectiveness of nirmatrelvir and ritonavir should be assessed individually for each of the four patient subgroups because this would provide a more robust assessment. The PBAC noted the weighted effective DPMQ could then be calculated based on the assumed distribution of patients across populations as shown in Table 26.
- 7.14 As described by the ESC, it was noted that regardless of whether the sponsor's analysis or the evaluation model was used, the ICERs for nirmatrelvir and ritonavir in patients aged 50-69 years were substantially higher than those calculated for the other patients groups (Table 19, Table 20). The PBAC noted that the ICER for use of nirmatrelvir and ritonavir in patients aged 50-69 with ≥ 1 additional risk factor is substantially higher than the corresponding population limited to patients with ≥ 2 additional risk factors (paragraph 6.71). On this basis, the PBAC considered that the PBS restriction for patients aged 50-69 years should revert to requiring at least 2 additional risk factors as described in paragraph 7.3, however the ICER for this subgroup remained higher than other subgroups even after the change to require at least 2 additional risk factors (Table 20).
- 7.15 Based on the available clinical evidence, the PBAC considered that a reduction in price from the current price would be required. The rationale for the requested price reduction was to overcome the uncertainty in cost-effectiveness arising from, in the main, varying modelled benefits in the target populations, which resulted in a range of ICERs. As noted in paragraph 7.9, the treatment effect of nirmatrelvir and ritonavir in practice appeared to be less than what was expected at the time it was recommended for inclusion on the PBS based on the results of EPIC-HR.
- 7.16 The PBAC agreed with the ESC that the single study by Xie et al did not justify an assumption of a reduced incidence of long COVID following treatment in the economic evaluation.
- 7.17 The PBAC noted the uncertainties in the submission's economic evaluation described by the ESC (paragraphs 6.76 to 6.79). The PBAC considered that the submission did not demonstrate cost-effectiveness due to concerns about the inputs applied in the resubmission's model. However the revised economic analysis based on a simplified model, showed that nirmatrelvir and ritonavir could be considered cost-effective if price were to be reduced such that the ICER does not exceed \$15,000/QALY in any of the patient subgroups (Table 25). The PBAC noted that the effective DPMQ required

for each individual population to achieve this ICER threshold in all subgroups and the overall weighted DPMQ shown in Table 26.

- 7.18 Noting the limitations of the data available, the PBAC also considered the multivariate sensitivity analysis presented in Table 27. The PBAC advised that the more favourable assumptions examined in the MSA were not accepted and did not provide reliable estimates for decision making.
- 7.19 In the context of the recommended changes to the restriction that remove access for patients aged 50-69 with only one additional risk factor (see paragraph 7.5), the PBAC considered that the proposed restriction would appropriately identify patients at high risk of severe disease requiring hospitalisation. The PBAC considered that consistent with its previous advice, the appropriate use of nirmatrelvir and ritonavir in patients at high risk of severe disease would significantly reduce the risks of hospitalisation and death from COVID-19 (meta-analyses conducted during the evaluation, refer Figure 4 to Figure 7), however the magnitude of benefit was uncertain given that the treatment effect of nirmatrelvir and ritonavir in practice appeared to be less than the results of EPIC-HR (see paragraph 6.25).
- 7.20 The PBAC advised that a price increase was not justified by the evidence presented in the submission due to the concerns outlined in paragraphs 7.9 to 7.16 and therefore the PBAC advised that it did not support a price higher than the current DPMQ (\$1,114.84) for nirmatrelvir and ritonavir.
- 7.21 The PBAC advised that on the basis of the revised economic evaluation, a price reduction is necessary to demonstrate cost-effectiveness based on an indicative ICER of \$15,000/QALY. On this basis, the PBAC recommended that a price reduction in the order of |% to |% from the current DPMQ would be required for nirmatrelvir and ritonavir (Table 25).
- 7.22 The PBAC noted the submission had assumed similar rates of COVID-19 and similar rates of use of antivirals for COVID-19 as has occurred in the past, which likely over-estimated costs in the short-term, although this was unclear over the medium term. The submission assumed market the share of nirmatrelvir and ritonavir would increase from |% to |% by 2027, which was likely to result in the financial estimates being overestimated. The PBAC considered the current market share of nirmatrelvir and ritonavir of approximately 40% to be an underestimate of the achievable proportion, however considered that peak market share for nirmatrelvir and ritonavir was unlikely to exceed 70%, and it would take time to see this adjustment. The PBAC noted published studies reported that approximately 15% of the population had a possible contraindication to nirmatrelvir and ritonavir (paragraph 4.5). The PBAC noted that the market share for nirmatrelvir and ritonavir may be impacted by its advice in relation to molnupiravir at the November 2023 meeting.
- 7.23 The PBAC noted that the estimated utilisation and financial estimates were uncertain, and dependent on future patterns of antiviral usage and relative usage of nirmatrelvir and ritonavir compared with the alternative treatment (molnupiravir). The PBAC

considered that any set of estimates of future expenditure for treatments for COVID 19 will be associated with a high level of uncertainty due to the unknown characteristics of future COVID-19 variants e.g., transmissibility, severity of symptoms and risk of hospitalisation and due to unpredictable developments such as availability of new treatments and vaccines.

- 7.24 The PBAC recommended that the sponsor and Department explore initiatives to support the safe and effective use of oral antiviral medicines for COVID-19, consistent with quality use of medicines (QUM) principles. The PBAC noted that clinical considerations may include selecting the best option from the range available taking into account the clinical condition, risks and benefits for the patient, their co-morbidities, other therapies and monitoring considerations.
- 7.25 In view of the uncertain financial estimates, the PBAC considered that the listing of nirmatrelvir and ritonavir should be considered again after 3 years. The PBAC requested that the DUSC conduct a review of OAV utilisation for PBAC consideration in July 2026. The PBAC requested that the sponsor provide an update on the effectiveness, safety and cost-effectiveness of nirmatrelvir and ritonavir alongside the abovementioned DUSC review to support the PBAC consideration in July 2026.
- 7.26 The PBAC noted that the opportunity cost of expenditure on oral antivirals is substantial, given that current expenditure on these agents currently accounts for 5% of the total PBS budget (before rebates). This significant allocation of resources to oral antivirals for COVID-19 has the potential to limit the ability of the government to fund other potentially beneficial treatments (Molnupiravir Public Summary Document, July 2023 meeting, paragraph 6.83).
- 7.27 The PBAC noted that this submission is not eligible for an Independent Review as it was not seeking an additional indication for nirmatrelvir and ritonavir on the PBS.

Outcome:

Advice Provided

8 Recommended listing

- 8.1 Amend existing listing as follows:

Additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NIRMATRELVIR (&) RITONAVIR				
Authority Required (STREAMLINED)				
nirmatrelvir 150 mg tablet [4] (&) ritonavir 100 mg tablet [2], 5 x 6	1	1	0	Nirmatrelvir and ritonavir
Prescriber bag				
nirmatrelvir 150 mg tablet [4] (&) ritonavir 100 mg tablet [2], 5 x 6	2	2	0	Nirmatrelvir and ritonavir

Restriction for nirmatrelvir and ritonavir for patients aged ≥ 70 years

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria: Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
The treatment must be initiated within 5 days of symptom onset; OR The treatment must be initiated as soon as possible after a diagnosis is confirmed where asymptomatic.
Population criteria: Patient must be at least 70 years of age.
Prescribing Instructions: Access to this drug through this restriction is permitted irrespective of vaccination status. Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record. Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record. This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.
Caution: <i>Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Nirmatrelvir and ritonavir Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.</i>
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

Restriction for nirmatrelvir and ritonavir for patients who are immunocompromised or have previously experienced a COVID-19 infection resulting in hospitalisation

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria: Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must have at least one sign or symptom attributable to COVID-19
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
Patient must satisfy at least one of the following criteria: (i) be moderately to severely immunocompromised with risk of progression to severe COVID-19 disease due to the immunocompromised status, (ii) has experienced past COVID-19

infection resulting in hospitalisation,
AND
The treatment must be initiated within 5 days of symptom onset
AND
Patient must be at least 18 years of age.
<p>Prescribing Instructions:</p> <p>For the purpose of administering this restriction, 'moderately to severely immunocompromised' patients are those with:</p> <ol style="list-style-type: none"> Any primary or acquired immunodeficiency including: <ol style="list-style-type: none"> Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders, Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months), Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency; OR Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received: <ol style="list-style-type: none"> Chemotherapy or whole body radiotherapy, High-dose corticosteroids (at least 20 mg of prednisone per day, or equivalent) for at least 14 days in a month, or pulse corticosteroid therapy, Biological agents and other treatments that deplete or inhibit B cell or T cell function (abatacept, anti-CD20 antibodies, BTK inhibitors, JAK inhibitors, sphingosine 1-phosphate receptor modulators, anti-CD52 antibodies, anti-complement antibodies, anti-thymocyte globulin), Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) including mycophenolate, methotrexate, leflunomide, azathioprine, 6-mercaptopurine (at least 1.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus); OR Any significantly immunocompromising condition(s) where, in the last 12 months the patient has received an anti-CD20 monoclonal antibody treatment, but criterion 2c above is not met; OR Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies; OR People with disability with multiple comorbidities and/or frailty. <p>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.</p> <p>For the purpose of administering this restriction, signs or symptoms attributable to COVID-19 are: fever greater than 38 degrees Celsius, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell.</p> <p>Access to this drug through this restriction is permitted irrespective of vaccination status.</p> <p>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.</p> <p>Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.</p> <p>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.</p> <p>Caution: <i>Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Nirmatrelvir and ritonavir Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.</i></p> <p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p> <p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>

Restriction for nirmatrelvir and ritonavir for Aboriginal and Torres Strait Islander people

Category / Program: General Schedule

Public Summary Document – November 2023 PBAC Meeting

Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria:
Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must have at least one sign or symptom attributable to COVID-19
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
The treatment must be initiated within 5 days of symptom onset
Population criteria:
Patient must be each of: (i) identify as Aboriginal or Torres Strait Islander, (ii) at least 30 years of age, (iii) at high risk.
Prescribing Instructions:
For the purpose of administering this restriction, high risk is defined as the presence of at least one of the following conditions:
<ol style="list-style-type: none"> 1. The patient is in residential aged care 2. The patient has disability with multiple comorbidities and/or frailty 3. Neurological conditions, including stroke and dementia and demyelinating conditions 4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease 5. Heart failure, coronary artery disease, cardiomyopathies 6. Obesity (BMI greater than 30 kg/m²) 7. Diabetes type I or II, requiring medication for glycaemic control 8. Renal impairment (eGFR less than 60mL/min) 9. Cirrhosis 10. The patient has reduced, or lack of, access to higher level healthcare and lives in an area of geographic remoteness classified by the Modified Monash Model as Category 5 or above 11. Past COVID-19 infection episode resulting in hospitalisation.
Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.
For the purpose of administering this restriction, signs or symptoms attributable to COVID-19 are: fever greater than 38 degrees Celsius, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell.
Access to this drug through this restriction is permitted irrespective of vaccination status.
Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.
Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.
This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.
Administrative Advice: The Modified Monash Model categorises an area according to geographical remoteness and town size. Details can be found at: https://www.health.gov.au/health-topics/rural-health-workforce/classifications/mmm
Caution:
Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Nirmatrelvir and ritonavir Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.

Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

Restriction for nirmatrelvir and ritonavir for patients aged 50 - 69 years with ~~one~~ two risk factors

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Indication: SARS-CoV-2 infection
Clinical criteria:
Patient must have received a positive polymerase chain reaction (PCR) test result; OR Patient must have received a positive rapid antigen test (RAT) result
AND
Patient must have at least one sign or symptom attributable to COVID-19
AND
Patient must not require hospitalisation for COVID-19 infection at the time of prescribing
AND
The treatment must be initiated within 5 days of symptom onset
Population criteria:
Patient must be at high risk of requiring hospitalisation for COVID-19 infection Patient must be both: (i) at least 50 years of age, (ii) at high risk.
AND
Patient must be at least 50 years old, but not older than 60 years; or Patient must be at least 60 years old, but not older than 70 years
Prescribing Instructions:
For the purpose of administering this restriction, high risk is defined as the presence of at least one of the following conditions:
1. The patient is in residential aged care
2. The patient has disability with multiple comorbidities and/or frailty
3. Neurological conditions, including stroke and dementia and demyelinating conditions
4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease
5. Heart failure, coronary artery disease, cardiomyopathies
6. Obesity (BMI greater than 30 kg/m²)
7. Diabetes type I or II, requiring medication for glycaemic control
8. Renal impairment (eGFR less than 60mL/min)
9. Cirrhosis
10. The patient has reduced, or lack of, access to higher level healthcare and lives in an area of geographic remoteness classified by the Modified Monash Model as Category 5 or above
11. Past COVID-19 infection episode resulting in hospitalisation.
Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.
For the purpose of administering this restriction, signs or symptoms attributable to COVID-19 are: fever greater than 38 degrees Celsius, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell.
Access to this drug through this restriction is permitted irrespective of vaccination status.
Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.
Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.

~~This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.~~

For the purpose of administering this restriction, high risk is defined as either a past COVID-19 infection episode resulting in hospitalisation, or the presence of at least two of the following conditions:

1. The patient is in residential aged care,
2. The patient has disability with multiple comorbidities and/or frailty,
3. Neurological conditions, including stroke and dementia and demyelinating conditions,
4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease,
5. Heart failure, coronary artery disease, cardiomyopathies,
6. Obesity (BMI greater than 30 kg/m²),
7. Diabetes type I or II, requiring medication for glycaemic control,
8. Renal impairment (eGFR less than 60mL/min),
9. Cirrhosis, or
10. The patient has reduced, or lack of, access to higher level healthcare and lives in an area of geographic remoteness classified by the Modified Monash Model as Category 5 or above.

Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records. For the purpose of administering this restriction, signs or symptoms attributable to COVID-19 are: fever greater than 38 degrees Celsius, chills, cough, sore throat, shortness of breath or difficulty breathing with exertion, fatigue, nasal congestion, runny nose, headache, muscle or body aches, nausea, vomiting, diarrhea, loss of taste, loss of smell.

Access to this drug through this restriction is permitted irrespective of vaccination status.

Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.

Where a RAT is used to confirm diagnosis, available information about the test result, testing date, location and test provider (where relevant) must be recorded on the patient record.

This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.

Note

The Modified Monash Model categorises an area according to geographical remoteness and town size. Details can be found at: <https://www.health.gov.au/health-topics/rural-health-workforce/classifications/mmm>

Caution:

Nirmatrelvir with ritonavir has significant drug-drug interactions. Please refer to the TGA approved Nirmatrelvir and ritonavir Product Information. Prescribers and dispensers should carefully review a patient's concomitant medications including over-the-counter medications, herbal supplements, and recreational drugs.

Administrative Advice: No increase in the maximum quantity or number of units may be authorised.

Administrative Advice: No increase in the maximum number of repeats may be authorised.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

It was Pfizer's understanding that the PBAC considered access for patients aged 50-69 years with one additional risk factor to be temporary. Scenarios were presented in the initial submission on that basis, in order to facilitate a recommendation based on an understanding of the cost-effectiveness of Paxlovid across all current populations. Pfizer is committed to a smooth transition and is working collaboratively with the Australian Government to ensure continued broad and equitable access to this medicine for all eligible patients.