An addendum to this public summary document has been included at the end of the document.

# 4.01 MOLNUPIRAVIR, Capsule 200 mg, Lagevrio®, Merck Sharp & Dohme (Australia) Pty Ltd.

## 1 Purpose of submission

1.1 The Category 2 submission from Merck Sharp & Dohme (Australia) Pty Ltd (hereafter MSD) has requested maintenance of a 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.

1.2 Molnupiravir was included on the Pharmaceutical Benefits Scheme (PBS) on 1 March 2022 following consideration of an independent rapid health technology assessment (rHTA) by the Pharmaceutical Benefits Advisory Committee (PBAC) at an out-of-session meeting in February 2022. The primary source of evidence at the time was the MOVe-OUT trial. On the basis of the clinical and economic analyses included in the report of the rHTA, the PBAC was satisfied that molnupiravir (added to usual care) was likely to provide, for some patients, a significant improvement in efficacy over usual care (i.e., symptomatic management of COVID-19) in terms of a reduction in the risk of developing severe disease requiring admission to hospital. Molnupiravir was listed on the basis of a cost-effectiveness analysis comparing molnupiravir (added to usual care) to usual care (without use of antiviral treatments). At the time of the PBAC's original consideration of molnupiravir, nirmatrelvir and ritonavir (Paxlovid®) had not been considered by the PBAC for inclusion on the PBS. Molnupiravir was thus the first oral antiviral listed on the PBS for patients with symptomatic COVID-19 at high risk of developing severe disease that necessitated hospitalisation.

1.3 The purpose of the current submission was to meet the requirements of the original PBAC assessment, which requested that the sponsor provide a 'a full update on the effectiveness, safety and cost-effectiveness of molnupiravir when used in patients who are eligible to receive this medicine under the PBS no later than the cut-off for the July 2023 PBAC meeting'.

1.4 The original listing of molnupiravir on the PBS limited use to three populations with mild to moderate COVID-19 who were considered to be at higher risk of developing severe disease requiring hospitalisation:

(i) people aged ≥ 65 years with two or more risk factors

(ii) people aged ≥ 18 years who are moderately to severely immunocompromised and at risk of progression to severe disease, and

(iii) Aboriginal or Torres Strait Islander people aged ≥ 50 years with two or more risk factors.

1.5 Over time, the PBAC recommended various changes to the PBS listing of molnupiravir. Of particular relevance to the consideration of this submission, the PBAC, at its meeting in November 2022[1] reviewed outcomes from several additional studies of the use of molnupiravir and concluded that although nirmatrelvir and ritonavir may be preferred for many patients with mild to moderate COVID-19 at high risk of progression to severe disease, in many common clinical circumstances nirmatrelvir and ritonavir will be contraindicated or unsuitable for use, and molnupiravir remained a suitable option in such patients. On this basis, the PBAC recommended that an administrative note should be added to the PBS listing of molnupiravir stating that molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable. The administrative note was incorporated into the listing in January 2023. The submission noted that the absence of a definition for the phrase 'contraindicated or otherwise unsuitable' leaves the phrase open to a broad range of interpretations. The PBAC noted that, given the time pressures general practitioners face, it would not be unreasonable to expect that GPs sometimes prescribe molnupiravir when a patient is on any therapy that could potentially interact with nirmatrelvir and ritonavir even though it may be possible to manage the potential for an interaction.

1.6 Since February 2023, molnupiravir has been listed for the following populations with mild to moderate COVID-19 who are at high risk of developing severe disease requiring hospitalisation:

(i) people aged ≥ 70 years (hereafter, '70+' subgroup);

(ii) people aged ≥ 50 years with two or more risk factors or a past COVID-19 infection episode resulting in hospitalisation (hereafter '50-69 high risk' subgroup);

(iii) 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 and subsequently reinfected (hereafter 'IC or previously hospitalised' subgroup); and

(iv) Aboriginal or Torres Strait Islander people aged ≥ 30 years with one or more risk factors (hereafter 'Indigenous high risk' subgroup).

[1] November 2022 PBAC Outcome Statement, COVID-19 Antiviral Restrictions, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2022-11/covid-19-oral-treatments-outcome-nov-2022.pdf

1.7 Table 1 summarises the key components of the clinical issue addressed by the submission. The submission sought continued listing of molnupiravir for the four populations for which it is currently listed on the basis of a cost-effectiveness analysis versus usual care excluding use of antiviral treatments. The submission also assumed continuation of the prescriber bag listing of molnupiravir.

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

| Component | Description |
|---|---|
| Population | Patients with mild to moderate COVID-19 who are considered to be at higher risk of developing severe disease requiring hospitalisation:<br>i) people aged ≥ 70 years;<br>ii) people aged ≥ 50 years with two or more risk factors or a past COVID-19 infection episode resulting in hospitalisation;<br>iii) 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; and<br>iv) Aboriginal or Torres Strait Islander people aged ≥ 30 years with one or more risk factors. |
| Intervention | Molnupiravir 800 mg (4 x 200 mg capsules) taken orally every 12 hours for five days |
| Comparator | Main: usual care excluding use of antiviral treatments<br>Supplementary: nirmatrelvir and ritonavir (Paxlovid®) |
| Outcomes | Risk of hospitalisation or death<br>Time to recovery of acute COVID-19<br>Viral load |
| Clinical claim | Molnupiravir is superior to usual care (excluding use of antiviral treatments) in reducing the risk of hospitalisation and death with an inferior but manageable safety profile.<br><br>The submission claims that it is inconclusive and uncertain as to whether molnupiravir or nirmatrelvir and ritonavir is more effective than the other in reducing the risk of hospitalisation or death. The submission claims that, in the real world setting, molnupiravir is a safer option compared to nirmatrelvir and ritonavir. |

Abbreviations: mg = milligrams
Source: Table 1.1-5 (p11) of the submission

# 2 Background

## *Registration status*

2.1 Molnupiravir was granted provisional approval by the TGA on 20 January 2022 for the treatment of adults with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk for hospitalisation or death. Provisional approval was granted for a two-year period, with the consent to import or supply molnupiravir effective until 18 January 2024. The submission has advised that the sponsor intends to submit an extension to the provisional registration in July 2023. The pre-PBAC response stated that MSD was still in discussions with the TGA in regard to the regulatory submission plan.

2.2 The U.S. Food and Drug Administration (FDA) issued an emergency use authorisation (EUA) in December 2021 for the emergency use of molnupiravir. It has emergency use authorisation for the treatment of adults with a current diagnosis of mild-to-moderate COVID-19:

- who are at high risk for progression to severe COVID-19, including hospitalisation or death, and
- for whom alternative COVID-19 treatment options approved or authorised by FDA are not accessible or clinically appropriate.[2]

2.3 The European Medicines Agency (EMA), in February 2023, recommended the refusal of the marketing authorisation for molnupiravir. The EMA considered that it was not possible to conclude that molnupiravir can reduce the risk of hospitalisation or death or shorten the duration of illness or time to recovery in adults at risk of severe disease. Furthermore, the EMA considered that it was not possible to identify a specific group of patients in whom a clinically relevant benefit of molnupiravir could be demonstrated.[3] The submission noted that the sponsors of molnupiravir in Europe had requested a re-examination of EMA's opinion. On 27 June 2023, the EMA announced that the EU application for marketing authorization of molnupiravir had been withdrawn[4]. The Australian sponsor of molnupiravir notified the Department of the withdrawal on 28 June 2023.

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

# 3 Requested listing

3.1 The submission requested continued reimbursement of molnupiravir for the four high risk populations for which it was currently PBS-listed. No changes to the current restrictions, maximum quantity or number of repeats were proposed. The only change proposed to the current listing was a reduction in the effective ex-manufacturer price by means of introduction of a special pricing arrangement (such that there be no change to the published dispensed prices of molnupiravir). The current approved ex-manufacturer price (AEMP) is $988 for a pack of 40 capsules. The current submission proposed an effective ex-manufacturer price of $, which reflecting approximately % reduction in the effective ex-manufacturer price.

[2] https://www.fda.gov/media/155054/download

[3] https://www.ema.europa.eu/documents/smop-initial/questions-answers-refusal-marketing-authorisation-lagevrio-molnupiravir_en.pdf

[4] https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-withdrawal-application-marketing-authorisation-lagevrio-molnupiravir_en.pdf

**Table 2: Essential elements of the proposed listing of molnupiravir**

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price for Max. Qty | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| MOLNUPIRAVIR | | | | | |
| Authority Required (STREAMLINED) | | | | | |
| Molnupiravir 200 mg capsule, 40 | $1,109.39 published price<br>$[redacted] effective price | 1 | 40 | 0 | Lagevrio |
| Prescriber bag | | | | | |
| Molnupiravir 200 mg capsule, 40 | $2,191.42 published price<br>$[redacted] effective price[a] | 2 | 80 | 0 | Lagevrio |

a. An incorrect Administration, Handling and Infrastructure (AHI) fee was applied in the calculation of the effective dispensed price for the prescriber bag listing in the submission. This was corrected during the evaluation.
Source: Table 1.4-1 p24 of the submission

**Table 3: Restrictions applying for molnupiravir**

| |
|---|
| **Category / Program:** General Schedule |
| **Prescriber type:** ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐ |
| **Restriction type:**<br>☒Authority Required (STREAMLINED) |
| **Administrative Advice:**<br>Note: No increase in the maximum quantity or number of units may be authorised.<br>Note: No increase in the maximum number of repeats may be authorised.<br>Note: This drug should be considered for use only if nirmatrelvir (&) ritonavir is contraindicated or otherwise unsuitable.<br>*Note: Special Pricing Arrangements apply* |
| **Indication:** SARS-CoV-2 infection |
| **13759** |
| **Indication:** SARS-CoV-2 infection |
| **Clinical criteria:** |
| Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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<br>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. |
| Access to this drug through this restriction is permitted irrespective of vaccination status.<br>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.<br>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.<br>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection. |
| **13824** |
| **Indication:** SARS-CoV-2 infection |
| **Clinical criteria:** |
| Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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. |
| **Population criteria:** |
| Patient must be at least 18 years of age. |
| For the purpose of administering this restriction, 'moderately to severely immunocompromised' patients are those with:<br>1. Any primary or acquired immunodeficiency including:<br>a. Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders,<br>b. Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),<br>c. Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency; OR<br>2. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received:<br>a. Chemotherapy or whole body radiotherapy,<br>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,<br>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),<br>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<br>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<br>4. Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies; OR<br>5. People with disability with multiple comorbidities and/or frailty.<br><br>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.<br>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.<br>Access to this drug through this restriction is permitted irrespective of vaccination status.<br>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.<br>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.<br>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection. |
| **13748** |
| **Indication:** SARS-CoV-2 infection |
| **Clinical criteria:** |
| Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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, |

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|---|
| **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. |
| For the purpose of administering this restriction, high risk is defined as the presence of at least one of the following conditions:<br>1. The patient is in residential aged care<br>2. The patient has disability with multiple comorbidities and/or frailty<br>3. Neurological conditions, including stroke and dementia and demyelinating conditions<br>4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease<br>5. Heart failure, coronary artery disease, cardiomyopathies<br>6. Obesity (BMI greater than 30 kg/$m^2$)<br>7. Diabetes type I or II, requiring medication for glycaemic control<br>8. Renal impairment (eGFR less than 60mL/min)<br>9. Cirrhosis<br>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<br>11. Past COVID-19 infection episode resulting in hospitalisation.<br><br>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.<br>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.<br>Access to this drug through this restriction is permitted irrespective of vaccination status.<br>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.<br>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.<br>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.<br>**Note**<br>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 |
| **13765** |
| **Indication:** SARS-CoV-2 infection |
| **Clinical criteria:** |
| Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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 both: (i) at least 50 years of age, (ii) at high risk. |
| 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:<br>1. The patient is in residential aged care,<br>2. The patient has disability with multiple comorbidities and/or frailty,<br>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/m$^2$),
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

3.2 The restriction includes an administrative note stating this drug should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable. The pre-PBAC response stated that molnupiravir is being appropriately prescribed, in line with this administrative note and associated guidelines, and suggested that formalisation of the note as a clinical criterion was impractical and could put patient safety at risk. The response stated that more than half of the patients in the proposed population receive medicines that are contraindicated for use with nirmatrelvir and ritonavir and that many patients are on multiple medicines; noting that 17% of patients on molnupiravir are on > 10 medicines. The response also described patients with complex needs and comorbidities, such as cognitive decline, and polypharmacy and stated these patients are not suitable for complicated instructions on stopping and restarting drugs with relative contraindications. The response stated that molnupiravir was preferentially distributed to care homes due to these complexities. The response stated that any formalisation would risk patient safety by suggesting to GPs that they must manage the multiple contraindicated medicines their patients are taking.

3.3 The submission requested removal of the administrative note that indicates that molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable, in the event that the PBAC determined nirmatrelvir and ritonavir to be the appropriate main comparator.

3.4 The PBAC considered that the administrative note should be formalised in the restriction to provide greater clarity to prescribers on the appropriate population for molnupiravir (see paragraph 7.12).

*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. 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 Molnupiravir is a prodrug that is metabolised to n-hydroxycytidine (NHC) which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase results in an accumulation of errors in the viral genome leading to inhibition of replication.

4.3 Molnupiravir 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 that necessitates hospitalisation.

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

# 5 Comparator

5.1 The submission nominated usual care (i.e., symptomatic management of COVID-19) as the main comparator on the grounds that the intent of the administrative note added to the restriction for molnupiravir in January 2023 positions molnupiravir as a treatment for patients who are unable to be treated with nirmatrelvir and ritonavir.

5.2 Although the submission's arguments could be a reasonable justification for the nomination of usual care as the appropriate main comparator, as discussed in paragraph 1.5, the absence of a definition for the phrase 'contraindicated or otherwise unsuitable' in the restriction leaves the phrase open to a broad range of interpretations. Thus, there may be some use of molnupiravir in some patients in whom nirmatrelvir and ritonavir could actually be used. It has previously been reported that the numerous potential drug interactions with nirmatrelvir and ritonavir result in molnupiravir being the dominant antiviral being used to treat people aged

70 years or older, especially in care homes (Kidd & Kelly, 2022[5]). The submission assumed % market share for molnupiravir within the oral antiviral market in the financial estimates.

5.3 Although the submission stated that usual care was the only appropriate comparator for molnupiravir, it appropriately attempted to include a clinical comparison of molnupiravir and nirmatrelvir and ritonavir. Availability of alternative treatments such as remdesivir was not considered. The pre-PBAC response stated that MSD did not consider remdesivir as a relevant alternative, because it required daily IV administrations over at least 3 days.

5.4 The objective of treatment with nirmatrelvir and ritonavir is identical to the objective of treatment with molnupiravir i.e., the aim of treatment is to avoid hospitalisation and death in patients with mild to moderate COVID-19 who are at high risk of developing severe disease. In other words, the outcome sought to be purchased by funding of the treatments on the PBS is identical for molnupiravir and for nirmatrelvir and ritonavir. Thus, regardless of whether nirmatrelvir and ritonavir is the appropriate comparator for molnupiravir, nirmatrelvir and ritonavir could provide a valuable frame of reference for considering the relative cost-effectiveness of molnupiravir. The Pre-Sub-Committee Response (PSCR) maintained that usual care was the appropriate comparator and stated that nirmatrelvir and ritonavir should not be used as either a comparator or as a frame of reference due to the administrative note. The PSCR claimed that recent PBS market share data confirmed that molnupiravir is appropriately being used in patients in whom nirmatrelvir and ritonavir is not suitable, consistent with the administrative note (see paragraph 5.8).

5.5 The number of prescriptions that were processed for molnupiravir and for nirmatrelvir and ritonavir in the year ending 31 March 2023 are summarised in Table 4. Over this time, the number of PBS and RPBS supplies of molnupiravir has been 2.5 times greater than the number of supplies of nirmatrelvir and ritonavir however, as shown in Figure 1 and Figure 2, the ratio of the extent of use of molnupiravir : nirmatrelvir and ritonavir has been falling over time. In February and March 2023 (after the addition of the administrative note in January 2023), molnupiravir represented ~60% of the oral antiviral market (these data reflect the date of processing by Services Australia, rather than date of dispensing by pharmacists).

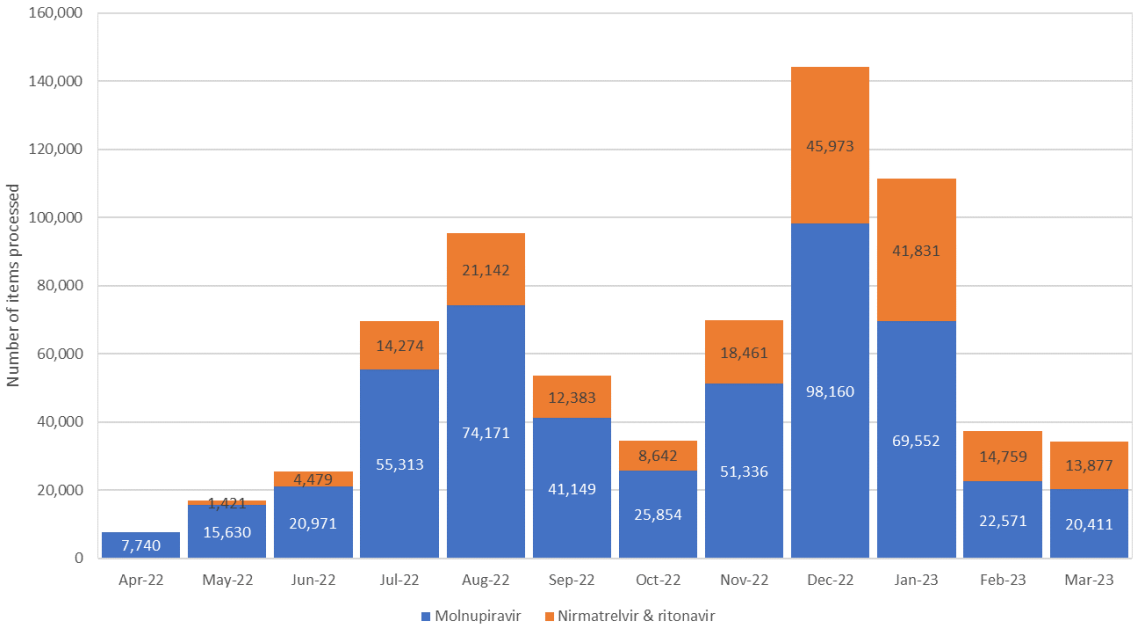
**Table 4: PBS supplies of molnupiravir and nirmatrelvir & ritonavir from 1 April 2022 to 31 March 2023**

| Drug | General | General safety net | Concession | Concession safety net | RPBS | RPBS safety net | Totals |
|---|---|---|---|---|---|---|---|
| Molnupiravir | 142,381 | 6,818 | 208,835 | 132,725 | 7,005 | 5,094 | 502,858 |
| Nirmatrelvir and ritonavir | 77,866 | 2,346 | 79,276 | 34,449 | 2,281 | 1,024 | 197,242 |

Source: analysis of data available at: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

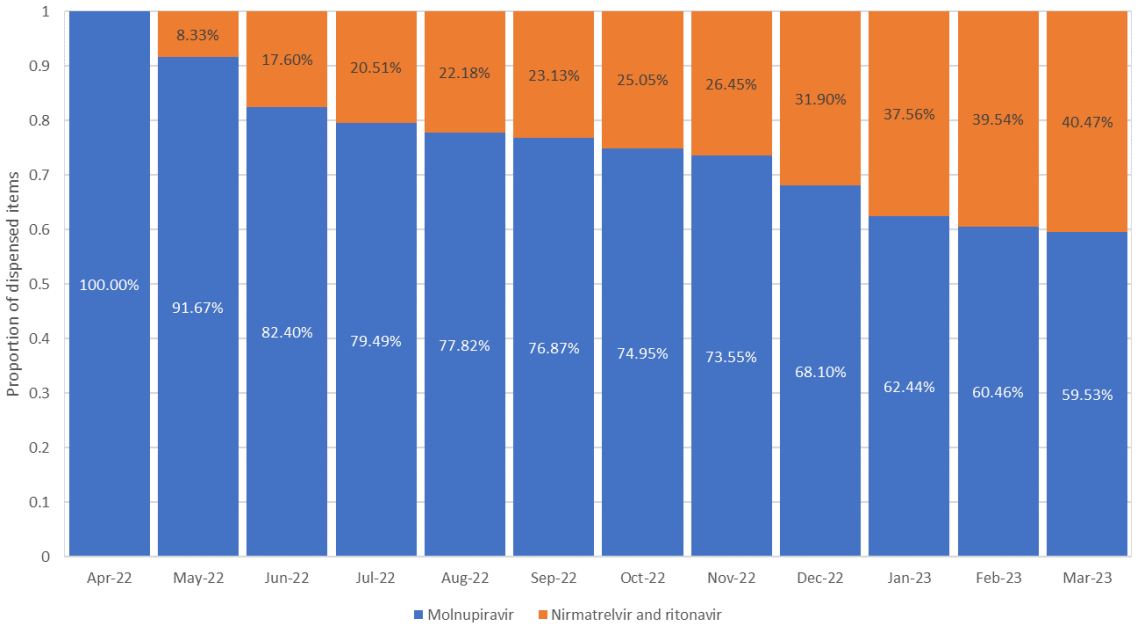
[5] Kidd MR, Kelly PM. PANORAMIC: important insights into molnupiravir use in COVID-19. *Lancet.* 2023; 401(10373):250-251 https://doi.org/10.1016/S0140-6736(22)02593-4

**Figure 1: PBS & RPBS items processed from 1 April 2022 to 31 March 2023**




Source: analysis of data available at: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

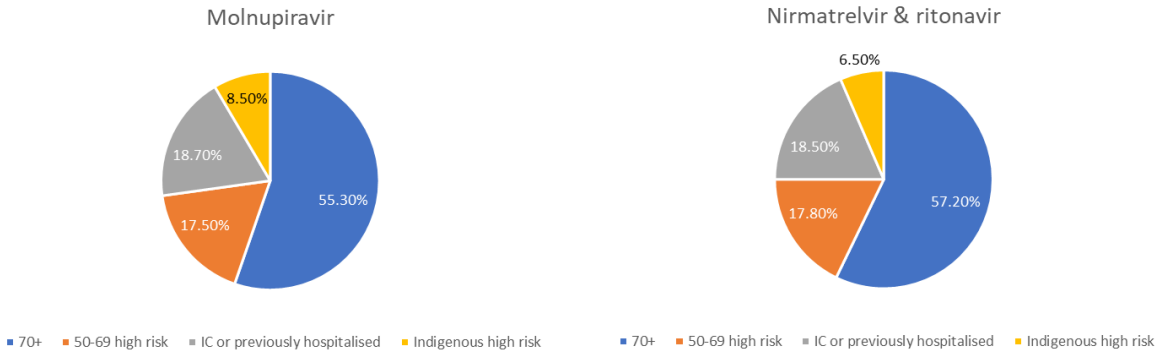
**Figure 2: Ratio of the extent of use of molnupiravir : nirmatrelvir and ritonavir from 1 May 2022 to 31 March 2023**




Source: analysis of data available at: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

5.6 The submission also provided the breakdown of prescriptions for molnupiravir and for nirmatrelvir and ritonavir by authority code over the period from August to December 2022 to inform the extent of use of each treatment by subgroup. As can be seen from Figure 3 that shows utilisation by PBS restriction, for both products, the majority of utilisation is in patients 70+ years of age.

**Figure 3: Distribution of prescriptions of molnupiravir and of nirmatrelvir and ritonavir by patient subgroup from August-December 2022**




Source: Analysis of data presented in Table 1.4-2, p27 of the submission

5.7 The PSCR stated that the administrative note has focused use of molnupiravir to patients not able to receive nirmatrelvir and ritonavir, noting that the market share of molnupiravir has reduced from > 70% to 56%. However, the PBAC noted that the market share of molnupiravir had already been declining prior to the introduction of the administrative note in January 2023 (Figure 3), likely due to factors such as publication of the PANORAMIC trial indicating that molnupiravir was less effective in practice than observed in the MOVe-OUT clinical trial. Other relevant factors may include increased prescriber experience with nirmatrelvir and ritonavir leading to improved ability to manage potential interactions, and expansion of the listing of nirmatrelvir and ritonavir.

5.8 The PSCR claimed that the observed market share of 56% was consistent with the estimated proportion of the population that is not able to receive nirmatrelvir and ritonavir based on a sponsor-led study presented as a poster at the International Congress of Infectious Diseases; Kuala Lumpur, Malaysia; November 17-20, 2022 (53.9%; reported by Cameron et al, 2022). However, the results could not be verified due to limited information reported in the poster. The analysis did not appear to distinguish between absolute contraindications as compared with relative contraindications that could be managed safely by the prescriber by temporarily adjusting the patient's other medications. The PBAC considered that although there is potential for a high proportion of patients to be at risk of a drug-drug interaction (DDI) with ritonavir (and therefore nirmatrelvir and ritonavir) based on their regular medication, the adjustment of their regular treatment schedule for the 5 days of treatment with nirmatrelvir and ritonavir may be possible to avoid potential DDI. The FDA briefing document referenced by the PSCR mentions that '…almost all of the 10 most common DDI drugs … could potentially be managed by holding the drug, adjusting the dose of the drug, or increased monitoring'[6].

[6] FDA Briefing document March 16, 2023. Page 38. https://www.fda.gov/media/166197/download

5.9 The PBAC noted that the National Clinical Evidence Taskforce (NCET), on the basis of results from the PANORAMIC trial, made a conditional recommendation against routine use of molnupiravir for treatment of patients with COVID 19[7]. The Taskforce states that 'there may be specific circumstances for the highest risk patients, where all other treatment options are contraindicated or inappropriate, in which non-routine use of molnupiravir might be considered, in consultation with specialist clinicians where necessary.'[8] The PBAC agreed with the ESC advice which noted that the prescriber community is becoming more able to distinguish absolute, from relative, contraindications and it is feasible that the change in utilisation estimates reflects a move towards a treatment pathway that is more consistent with the Taskforce's advice in practice.

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

# 6 Consideration of the evidence

## *Sponsor hearing*

6.6 The sponsor provided a recorded hearing for this item. The clinician discussed the impact of the COVID-19 pandemic on general practice including burnout, attrition, financial impacts, and low morale in the profession. It was noted that molnupiravir is simple to use in general practice, in comparison with nirmatrelvir and ritonavir, because the latter is associated with numerous potential drug interactions and may require more practitioner time for assessment and counselling and that short term medication changes were not suitable for some patients due to risk of confusion. The clinician discussed that oral antivirals, including molnupiravir, changed the face of the pandemic, and noted their beneficial impact, especially if used early, in shortening the course of illness, reducing severity, and preventing hospitalisations. The clinician described the benefits of molnupiravir for patients ineligible for nirmatrelvir and ritonavir. It was also noted that long COVID is a concern for the community.

## *Consumer comments*

6.7 The PBAC noted and welcomed the input from health care professionals (14), other interested individual (1) and organisations (3) via the Consumer Comments facility on the PBS website. Although many noted that effectiveness of molnupiravir may be less than nirmatrelvir and ritonavir, it was suggested that molnupiravir had a place in therapy as an alternative for those who could not take nirmatrelvir and ritonavir. Molnupiravir was described as well-tolerated with fewer drug interactions and contraindications for existing comorbidities, particularly amongst the elderly and those who are immunocompromised. Several inputs mentioned the ease of oral administration as an advantage over IV antivirals, enabling people to avoid hospital

[7] Source: https://clinicalevidence.net.au/wp-content/uploads/DECISION-TOOL-DT-FOR-ADULTS.pdf
[8] Source: https://app.magicapp.org/#/guideline/L4Q5An/rec/EPN8RW

attendance. Some discussed considering outcomes beyond hospitalisation and death and suggested that population health and quality of life may be improved, with reduced burden on the health system, if effects on viral load, infection and spread, and on long COVID amongst broader populations were considered. In vulnerable patients who have poor immune systems or are unvaccinated, molnupiravir was described as a highly effective therapy to prevent death or admission to hospital. Concerns were mentioned in relation to adjusting concomitant therapies, especially for immunocompromised patients and that molnupiravir would be used when a prescriber considered other medications could not be adjusted, even for a period of 5 days. Feedback mentioned some GPs may be reluctant to recommend changes to medicines prescribed in tertiary settings. Several inputs referred to emerging data on use in practice and provided links to recent publications. It was noted that protecting health system capacity has further benefit on health outcomes and lives saved, beyond the benefit to the individuals treated for COVID-19.

6.8 The input from the Kirby Institute, University of New South Wales (UNSW) stated that the benefit of nirmatrelvir and ritonavir was greater than molnupiravir, but both will have a substantial population health impact if accessible widely, including to younger people. The economic benefits of treating younger people include shorter time to recovery and viral clearance, meaning earlier return to work and reduced infectiousness. A substantial proportion of high risk people have contraindications to nirmatrelvir and ritonavir, and molnupiravir can be used as an alternative in such people.

6.9 The Lung Foundation Australia (LFA) described the health, financial and social cost of COVID-19 in Australia. The input noted that molnupiravir is recommended for treatment of COVID-19 when nirmatrelvir and ritonavir is unsuitable. The input outlined benefits of molnupiravir including that it can be taken at home, it allows patients to reduce their time of being unwell; reduce need for hospitalisation, no identified drug interactions allowing the patient to continue their other treatment options to maintain their health and wellbeing.

6.10 The Immunisation Coalition described molnupiravir as an important second line treatment and noted there is a relatively large proportion of older at risk people who cannot take first line treatment for COVID-19 because of drug interactions. The input cited medical literature supporting the role of molnupiravir including the cohort studies examining molnupiravir and risk of post-acute sequelae of COVID-19, such as published by Xie et al (2023)[9] and Hsu et al. (2023)[10] .

[9] Xie Y, Choi T, Al-Aly Z. Molnupiravir and risk of post-acute sequelae of covid-19: cohort study. BMJ. 2023 Apr 25;381:e074572. doi: 10.1136/bmj-2022-074572.

[10] Hsu WH, Shiau BW, Tsai YW, Wu JY, Liu TH, Chuang MH, Lai CC. The effect of molnupiravir on post-acute outcome of COVID-19 survivors. J Infect. 2023 Mar 21:S0163-4453(23)00145-7. doi: 10.1016/j.jinf.2023.03.016. Epub ahead of print.

## *Clinical studies*

6.11 The submission was based on evidence from:

- two randomised, controlled trials (RCTs) directly comparing molnupiravir to usual care;
- eight retrospective cohort studies assessing the comparative effectiveness of molnupiravir and/or nirmatrelvir and ritonavir to usual care (or to each other) in patients with COVID-19; and
- one indirect comparison of molnupiravir versus nirmatrelvir and ritonavir based on the sponsor-conducted RCTs conducted in non-hospitalised patients with COVID-19.

6.12 One additional RCT (EPIC-HR reported by Hammond 2022) investigating the efficacy and safety of nirmatrelvir and ritonavir in patients at high risk of developing severe COVID-19 and one additional potentially relevant retrospective cohort study (Wai 2022) were retrieved during the evaluation of the submission.

6.13 Details of the studies presented in the submission and the additional studies located during the evaluation are provided in Table 5.

**Table 5: Studies and associated reports presented in the submission and assessed in the Commentary**

| Study ID | Publication title | Publication citation |
|---|---|---|
| **RCTs** | | |
| MOVe-OUT | Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. | New England Journal of Medicine. 2022;386(6):509-20 |
| EPIC-HR | Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. | New England Journal of Medicine. 2022; 386(15):1397-1408 https://doi.org/10.1056/NEJMoa2118542 |
| PANORAMIC | Butler CC, Hobbs FR, Gbinigie OA, 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 |
| **Retrospective cohort studies** | | |
| Victorian dataset | Cowie B, Sutton B, Van Heer C, Majumdar S. Paxlovid is Australia's first-line COVID antiviral but Lagevrio also prevents severe disease in over-70s | The Conversation. 2022; https://theconversation.com/paxlovid-is-australias-first-line-covid-antiviral-but-lagevrio-also-prevents-severe-disease-in-over-70s-195349 |
| | Van Heer C, Majumdar, S, Parta I, et al. Effectiveness of Community-Based Oral Antiviral Treatments Against Severe COVID-19 Outcomes in Victoria, Australia, 2022: An Observational Study | Pre-print manuscript 2023; https://ssrn.com/abstract=4495142 |
| Arbel 2022 | Arbel R, Sagy YW, Battat E, et al Molnupiravir use and severe COVID-19 outcomes during the omicron surge. | Pre-print 2022; https://www.researchsquare.com/article/rs-2115769/v1 |

| Study ID | Publication title | Publication citation |
|---|---|---|
| Najjar-Debbiny 2022 | Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of molnupiravir in high-risk patients: A propensity score matched analysis. | Clinical Infectious Diseases. 2023;76(3):453-60. |
| Bajema 2022 | Bajema KL, Berry K, Streja E, et al. Effectiveness of COVID-19 treatment with nirmatrelvir-ritonavir or molnupiravir among US Veterans: target trial emulation studies with one-month and six-month outcomes. MedRxiv. 2022 Dec 6:2022-12. | Pre-print 2022; https://www.medrxiv.org/content/10.1101/2022.12.05.22283134v2 |
| Evans 2023 | Evans A, Qi C, Adebayo JO, et al. Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: a retrospective cohort study. | Journal of Infection. 2023;86(4):352-360 |
| Gentry 2023 | Gentry CA, Nguyen P, Thind SK, et al. Characteristics and outcomes of US Veterans at least 65 years of age at high risk of severe SARS-CoV-2 infection with or without receipt of oral antiviral agents. | Journal of Infection. 2023;86(3):248-255 |
| Wong 2022 | Wong CK, Au IC, Lau KT, 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):1213-22 |
| Yip 2022 | Yip TC, Lui GC, Lai MS, et al. Impact of the Use of Oral Antiviral Agents on the Risk of Hospitalization in Community Coronavirus Disease 2019 Patients (COVID-19). | Clinical Infectious Diseases. 2022; 76(3):e26-e33. |
| Wai 2023 | Wai AK, Chan CY, Cheung AW, et al. Association of Molnupiravir and Nirmatrelvir-Ritonavir with preventable mortality, hospital admissions and related avoidable healthcare system cost among high-risk patients with mild to moderate COVID-19. | The Lancet Regional Health – Western Pacific. 2022:100602. 2023;30:100602 https://doi.org/10.1016/j.lanwpc.2022.100602 |
| **Systematic review** | | |
| Lai 2022 | Lai CC, Wang YH, Chen KH, et l. The clinical efficacy and safety of anti-viral agents for non-hospitalized patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials. | Viruses. 2022;14(8):1706. |

Source: Table 2.2-1, pp37-38 of the submission

6.14 The key features of the studies listed in Table 5 are summarised in Table 6. The three RCTs are associated with a low risk of bias. Although the PANORAMIC trial was an open-label trial, the key outcomes of interest to this submission (i.e., rates of hospitalisation and death) are relatively objective outcomes. All of the observational studies could be considered to be associated with a high risk of bias given that all of studies were retrospective cohort studies and are thus subject to confounding due to potential for differences across treatment groups in unreported or unmeasured patient characteristics. The indirect comparison presented by Lai 2022 is also associated with a moderate risk of bias. Even though the analysis is based on outcomes of RCTs (MOVe-OUT trial for molnupiravir and the EPIC-HR trial for nirmatrelvir and ritonavir), as with any indirect comparison, there is a risk of differences in unreported or unmeasured patient characteristics in the two trials.

6.15 The submission described that although observational studies have a lower level of internal validity compared to RCTs, when properly designed to minimise confounding

and undertaken in the appropriate populations, they provide valuable information about the effectiveness of COVID-19 interventions in clinical practice, which may be particularly relevant for older populations. The submission suggested that the identified observational studies therefore provided a higher level of external applicability to the intended PBS population compared with the RCTs. The PBAC agreed with the ESC that the randomised trials for molnupiravir and nirmatrelvir and ritonavir (MOVe OUT and EPIC-HR, respectively) remained relevant to the assessment of the potential benefits and harms associated with these treatments, while acknowledging the concerns raised by the PBAC previously with respect to applicability of evidence (see paragraph 6.21).

**Table 6: Key features of the included evidence**

| Study | N | Setting | Design/ duration | Risk of bias | Patient population | Outcomes of interest | Use in modelled evaluation |
|---|---|---|---|---|---|---|---|
| MOVe-OUT | 1,433 | International | R, DB, MC 4 weeks follow-up May-Nov 2021 | Low | Non-hospitalised, unvaccinated adults with mild or moderate COVID and ≥1 risk factor diagnosed within 5 days of symptom onset | All cause hospitalisation or death | Not used |
| EPIC-HR | 2,246 | International | R, DB, MC 4 weeks follow-up Jul-Dec 2021- | Low | Non-hospitalised, unvaccinated adults with mild or moderate COVID and ≥1 risk factor diagnosed within 5 days of symptom onset | All cause hospitalisation or death | Not used |
| PANORAMIC | 25,054 | UK | R, OL, MC 4 weeks follow-up Dec 2021 – Apr 2022 | Low | Vaccinated and unvaccinated non-hospitalised adults aged ≥50 years (or ≥18 years with relevant comorbidities) diagnosed within 5 days of symptom onset | All cause hospitalisation or death | Source of symptom duration in the model |
| Victorian dataset | 38,933 | Victoria, Australia | Retrospective cohort 30 day follow up Diagnosed bwn Jul & Oct 2022- | High | Non-hospitalised, adults aged ≥70 years, diagnosed within 5 days of symptom onset | All cause hospitalisation or death | Primary source of treatment effect in the model for the 70+ & 50-69 high risk population |
| Arbel 2022 | 19,868 | Israel | Retrospective cohort 5 weeks follow up Jan-Mar 2022 | High | Vaccinated and unvaccinated, non-hospitalised adults ≥40 years diagnosed in an outpatient setting and not eligible for NMT/r with high risk of progression to severe COVID | COVID-19-related hospitalisation or death | Not used |

| Study | N | Setting | Design/ duration | Risk of bias | Patient population | Outcomes of interest | Use in modelled evaluation |
|---|---|---|---|---|---|---|---|
| Najjar-Debbiny 2022 | 5,322 | Israel | Retrospective cohort 4 weeks follow up Jan-Feb 2022 | High | 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 | Not used |
| Bajema 2022 | 1,794[a] 1,538[b] | US | Retrospective cohort 4 weeks follow up Jan-Feb 2022 | High | Vaccinated and unvaccinated, non-hospitalised adults ≥18 years at risk of severe COVID diagnosed in an outpatient setting | All cause hospitalisation or death | Not used |
| Evans 2023 | 5,332 | Wales | Retrospective cohort 180 days follow up Dec 2021-Apr 2022 | High | Vaccinated and unvaccinated, non-hospitalised adults diagnosed with higher-risk COVID infection | All cause hospitalisation or death | Source of baseline risk of hospitalisation and death and treatment effect in immune-compromised population |
| Gentry 2023 | 1,927 | US | Retrospective cohort 30 days follow up Jan-Feb 2022 | High | Vaccinated and unvaccinated adults aged ≥65 years diagnosed with mild to moderate COVID infection | All cause hospitalisation or death | Not used |
| Wong 2022 | 54,217 | Hong Kong | Retrospective cohort 4 weeks follow up Feb-Jun 2022 | High | 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 | Not used |
| Yip 2022 | 9,556 | Hong Kong | Retrospective cohort 30 days follow up Feb-Mar 2022 | High | Vaccinated and unvaccinated, non-hospitalised patients admitted within 5 days of symptom onset in an outpatient setting | All cause hospitalisation or death | Not used |
| Wai 2023 | 33,217[c] | Hong Kong | Retrospective cohort 4 weeks follow up Feb-Apr 2022 | High | Vaccinated and unvaccinated, non-hospitalised patients admitted within 5 days of symptom onset in an outpatient setting | Death | Not used |
| Lai 2022 | 3,679 | International | Indirect comparison using MOVe-OUT and EPIC-HR RCTs | Moderate | Non-hospitalised, unvaccinated adults with mild or moderate COVID and ≥1 risk factor diagnosed within 5 days of symptom onset | All cause hospitalisation or death | Not used |

Source: Table 2.3-1 on pp.43-46 of the submission; Wai 2023; Van Heer et al. (2023).

[a] for comparison of molnupiravir vs usual care
[b] for comparison of molnupiravir vs nirmatrelvir and ritonavir
[c] for the outpatient cohort
bwn = between; DB = double blind; MC = multi-centre; OL = open label; R = randomised; UK = United Kingdom; US = United States

6.16 There are several potential applicability issues with the majority of the studies presented in Table 6. In particular, the variation in the study periods examined by the studies could mean that the evidence is not 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 are not applicable to the Australian setting (e.g., if 'usual care' before and after hospitalisation is different to that experienced by patients in Australia, if the threshold for referring patients for admission to hospital are different to that applying in Australia).

## Comparative effectiveness

6.17 Table 7 summarises the results of the key comparisons provided by each of the studies. Odds ratios are unadjusted unless specified as being adjusted for covariates.

6.18 The results of the comparison of molnupiravir versus usual care, as presented in Table 7 are variable and there is thus substantial uncertainty around the extent of benefit associated with molnupiravir in terms of reduction in hospitalisations and death.

6.19 Examination of the studies where hospitalisations and deaths are reported separately indicates that both molnupiravir and nirmatrelvir and ritonavir reduce hospitalisations but that they also reduce the relative risk of death and do so to a greater extent than hospitalisations.

6.20 Initial information from a Victorian Department of Health data linkage project in patients ≥70 years of age was reported by Cowie et al (2022). At the time of preparing these minutes, the results of this analysis (described as the Victorian dataset) were available as a pre-print article by Van Heer et al. (2023) on the Lancet website[11], which had not yet been peer reviewed. The Victorian Department of Health had earlier provided the Commonwealth with results of these analyses on a confidential basis. The PBAC considered these real world data of interest, although noted that limited information was available during the evaluation and at the time of DUSC and ESC meetings (see paragraph 6.30).

[11] Van Heer, C. et al. (2023), Effectiveness of Community-Based Oral Antiviral Treatments Against Severe COVID-19 Outcomes in Victoria, Australia, 2022: An Observational Study. Available at SSRN: https://ssrn.com/abstract=4495142 or http://dx.doi.org/10.2139/ssrn.4495142

**Table 7: Key results from the studies presented in the submission**

| Study (and subgroup) | Endpoint | Molnupiravir n/N (%) | Usual care n/N (%) | Nirmatrelvir and ritonavir n/N (%) | OR molnupiravir vs usual care (95% CI) | OR nirmatrelvir and ritonavir vs usual care (95% CI) | OR molnupiravir vs nirmatrelvir and ritonavir (95% CI) |
|---|---|---|---|---|---|---|---|
| MOVe-OUT | Hospitalisation or death – Day 28 | 48/709 (6.8%) | 68/699 (9.7%) | n/a | **0.67 (0.46, 0.99)** | n/a | n/a |
| EPIC-HR | Hospitalisation or death – Day 28 | n/a | 66/1046 (6.3%) | 8/1039 (0.8%) | n/a | **0.12 (0.06, 0.24)** | n/a |
| Lai 2022 Indirect comparison based on MOVe-OUT and EPIC-HR | Hospitalisation or death – Day 28 | As presented in the above two rows | | | **0.67 (0.46, 0.99)** | **0.12 (0.06, 0.24)** | **5.85 (2.54, 13.46)** |
| PANORAMIC | Hospitalisation or death – Day 28 | 105/12529 (0.84%) | 98/12525 (0.78%) | n/a | 1.07 (0.81, 1.41) | n/a | n/a |
| PANORAMIC ≥ 65 years | Hospitalisation or death – Day 28 | NR | NR | n/a | 0.76 (0.46, 1.32) | n/a | n/a |
| PANORAMIC ≥ 80 years | Hospitalisation or death – Day 28 | NR | NR | n/a | 0.51 (0.16, 1.40) | n/a | n/a |
| Analyses presented in the manuscript Victorian dataset (≥ 70 years) | Hospitalised (subgroup[#]) | 195/15,673 (1.24%) | 185/10,637 (1.74%) | 46/4,823 (0.95%) | **0.71* (0.58, 0.87)** | **0.60* (0.43, 0.83)** | *1.18* (0.80, 1.74)* |
| | Hospitalised (full cohort) | 696/19,962 (3.49%) | 1,635/13,721 (11.92%) | 295/5,250 (5.62%) | NR* | NR* | *NC** |
| | Death (full cohort) | 346/19,962 (1.73%) | 462/13,721 (3.37%) | 29/5,250 (0.55%) | **0.45* (0.39, 0.53)** | **0.27* (0.18, 0.38)** | ***1.67* (1.11, 2.50)*** |
| Arbel 2022 | Hospitalisation – Day 35 | 26/1069 (2.43%) | 610/18799 (3.24%) | n/a | 0.74 (0.50, 1.11) | n/a | n/a |
| | Death – Day 35 | 8/1069 (0.75%) | 144/18799 (0.77%) | n/a | 0.98 (0.48, 2.00) | n/a | n/a |
| Arbel 2022 ≥ 65 years | Hospitalisation – Day 35 | 18/845 (2.13%) | 513/12724 (4.03%) | n/a | **0.52 (0.32, 0.83)** | n/a | n/a |
| | Death – Day 35 | 4/845 (0.47%) | 137/12724 (1.08%) | n/a | 0.44 (0.16, 1.18) | n/a | n/a |
| Najjar-Debbiny 2022 | Death or severe COVID-19 | 50/2661 (1.88%) | 60/2661 (2.25%) | n/a | 0.83 (0.57, 1.21) | n/a | n/a |
| Bajema 2022 | Hospitalisation or death – Day 30 | 40/897 (4.46%) | 51.9/897 (5.79%) | n/a | 0.75 (0.50, 1.16) | n/a | n/a |
| Bajema 2022 vs nirmatrelvir and ritonavir | Hospitalisation or death – Day 30 | 30/769 (3.90%) | n/a | 19/769 (2.47%) | n/a | n/a | 1.60 (0.89, 2.87) |
| Bajema 2022 >65 years | Hospitalisation or death – Day 30 | 30/543 (5.52%) | 44.3/538 (8.23%) | n/a | 0.66 (0.41, 1.06) | n/a | n/a |

| Study (and subgroup) | Endpoint | Molnupiravir n/N (%) | Usual care n/N (%) | Nirmatrelvir and ritonavir n/N (%) | OR molnupiravir vs usual care (95% CI) | OR nirmatrelvir and ritonavir vs usual care (95% CI) | OR molnupiravir vs nirmatrelvir and ritonavir (95% CI) |
|---|---|---|---|---|---|---|---|
| Bajema 2022 vs nirmatrelvir and ritonavir >65 years | Hospitalisation or death – Day 30 | 22/453 (4.9%) | n/a | 14/447 (3.1%) | n/a | n/a | 1.58 (0.80, 3.13) |
| Evans 2023 (immunocompromised) | Hospitalisation or death | 14/359 (3.90%) | 544/4973 (10.94%) | 17/602 (2.82%) | **0.33 (0.19, 0.56)** | **0.26 (0.16, 0.42)** | 1.40 (0.69, 2.83) |
| | | | | | **0.49^* (0.29, 0.83)** | **0.59^* (0.36, 0.97)** | 0.83^* (0.13, 5.45) |
| Gentry 2023 (≥ 65 years) | Hospitalisation or death – Day 30 | 31/557 (5.57%) | 139/1370 (10.15%) | 34/813 (4.19%) | **0.52 (0.35, 0.78)** | **0.39 (0.26, 0.57)** | 1.35 (0.82, 2.21) |
| Wong 2022 | Hospitalisation | 476/4983 (9.56%) | 4800/49234 (9.75%) | n/a | 0.98 (0.89, 1.0) | | |
| | Death | 45/4983 (0.91%) | 734/49234 (1.49%) | n/a | **0.61 (0.45, 0.82)** | | |
| Wong 2022 nirmatrelvir and ritonavir | Hospitalisation | n/a | 3107/54672 (5.68%) | 239/5542 (4.31%) | | **0.75 (0.65, 0.86)** | |
| | Death | n/a | 383/54672 (0.70%) | 9/5542 (0.17%) | | **0.23 (0.12, 0.44)** | |
| Indirect comparison based on Wong 2022 | Hospitalisation | | | | | | **1.31 (1.12, 1.52)** |
| | Death | | | | | | **2.66 (1.30, 5.43)** |
| Wong 2022 (> 60 years) | Hospitalisation | NR/4418 | NR/45415 | | **0.89^ (0.81, 0.97)** | | |
| | Death | NR/4418 | NR/45415 | | **0.75^ (0.60, 0.9)]** | | |
| Yip 2022 | Hospitalisation | 249/4798 (5.2%) | 214/4758 (4.5%) | 177/4921 (3.60%) | 1.16 (0.97, 1.40) | **0.68 (0.56, 0.83)** | **1.47 (1.21, 1.79)** |
| | | | | | 1.17^ (0.99, 1.39) | NR | **0.67^ (0.55, 0.81)** |
| | ICU admission, IMV use and/or death | 29/4798 (0.6%) | 24/4758 (0.5%) | 20/4921 (0.4%) | 1.20 (0.70, 2.07) | 0.67 (0.38, 1.18) | 1.50 (0.85, 2.67) |
| | | | | | 1.12^ (0.68, 1.82) | NR | 0.73^ (0.45, 1.49) |
| Yip 2022 (≥ 70 years) | Hospitalisation | NR/2541 | NR/2584 | NR/2693 | 1.15^ (0.95, 1.39)^ | NR | **0.68^ (0.54, 0.84)** |
| | ICU admission, IMV use and/or death | NR/2541 | NR/2584 | NR/2693 | 1.08^ (0.65, 1.82) | NR | 0.82^ (0.45, 1.49) |
| Wai 2023 (outpatients) | Death | 8/5345 (0.1%) | 65/23430 (0.2%) | 0/4442 (0%) | 0.54 (0.26. 1.11) | **0 (0, 0.31)** | **NC (1.73, ∞)** |

Sources: Table 2.5-2 (MOVe-OUT results) on p79 of the submission; Table 2.5-23 of the submission (EPIC-HR results), Table 2 Lai 2022 (results of pairwise indirect comparison based on MOVe-OUT and EPIC-HR); Table 2.5-4 of the submission (PANORAMIC results); Van Heer 2023 pre-print manuscript (Victorian dataset); Table 2.5-6 of the submission (Arbel 2022 results); Table 2.5-7 of the submission (Najjar-Debbiny 2022 results); Tables 2.5-8 and 2.5-17 of the submission (Bajema 2022 results), Tables 2.5-15 and text relating to secondary

analyses reported by the Evans 2023 manuscript (Evans 2023 results); Table 2.5-10 and deduction from information in Table 1 and Figure 2 in Gentry 2023 (Gentry 2023 results); Table 2.5-11 and analysis of information presented in the publication by Wong 2022 (Wong 2022 results), Tables 2.5-13 and 2.5-19 (Yip 2022 results); Wai 2023 (Wai 2023 results)
Abbreviations: CI = confidence interval; IMV = invasive mechanical ventilation; n/a = not applicable; NR = not reported; RR = relative risk
# 'subgroup' refers to the hospitalisation analysis cohort described in the manuscript and full cohort refers to the mortality analysis cohort described in the manuscript. The hospitalisation cohort is a subset of the mortality cohort and excludes patients in residential aged care facilities and those hospitalised on Day 0 or Day 1 after diagnosis of COVID-19
* Adjusted for nominated confounders
^ Adjusted hazard ratios. Note that hazard ratios <1 are favourable for the comparator in the analyses as these reflect time to the event.

### Pivotal randomised controlled trials – MOVe OUT and EPIC-HR

6.21 The PBAC considered that the randomised trials for molnupiravir and nirmatrelvir and ritonavir (MOVe OUT and EPIC-HR, respectively) remained relevant to the assessment of the potential benefits and harms associated with these treatments, while acknowledging the concerns it had raised previously[12][13] with respect to applicability of evidence from these trials to the PBS population given that vaccinations were not available at the time the trials were conducted so the vast majority of patients in the trials were unvaccinated and the uncertain impact of changes in circulating variants of the virus.

6.22 The PBAC recalled that it had previously considered the MOVe-OUT trial in February 2022 (see Table 8). Data from the final analysis of the study was less favourable to molnupiravir than the interim analysis for the primary endpoint (i.e., proportion of patients hospitalised or dead by Day 29 after randomisation).

**Table 8: Hospitalisation or death by Day 29 unadjusted results for: (i) patients captured by the interim analysis, (ii) additional patients beyond interim analysis, and (iii) the total population recruited to the MOVe-OUT trial**

| Population | Molnupiravir 800 mg | Placebo | Risk difference (95% CI) | Relative risk (95% CI) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Interim analysis | 28/385 (7.3%) | 53/377 (14.1%) | **−6.8% (−11.1%, −2.4%)** | **0.517 (0.335, 0.800)** | **0.479 (0.297, 0.774)** |
| Post-interim cohort | 20/324 (6.2%) | 15/322 (4.7%) | 1.5% (−2.0%, 5.0%) | 1.32 (0.691, 2.542) | 1.34 (0.684, 2.649) |
| Total patients (final analysis) | 48/709 (6.8%) | 68/699 (9.7%) | **−3.0% (−5.8%, −0.1%)** | **0.696 (0.488, 0.992)** | **0.674 (0.459, 0.989)** |

Statistically significant differences are shown in bolded typeface
The incremental cohort of patients that had been recruited to the MOVe-OUT trial but were not included in the interim analysis is referred to as the 'post-interim' cohort'.
Sources: Jayk Bernal, *NEJM*, 2021 (including supplement); available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2116044. Outcomes in additional patients calculated by deduction.

### PANORAMIC

6.23 PANORAMIC was an open-label, randomised controlled trial conducted in the UK in a community setting. Eligible participants were at least 50 years of age, or at least

[12] PBAC Web Outcome Statement molnupiravir February 2022, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/out-of-session/pbac-outcome-molnupiravir-february-2022.pdf
[13] PBAC Web Outcome Statement nirmatrelvir and ritonavir March 2022, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/out-of-session/pbac-web-outcome-nirmatrelvir-and-ritonavir-march-2022.pdf

18 years of age with relevant comorbidities, and were randomised within 5 days of confirmed COVID-19. The trial did not seek to study patients at highest risk of progression to severe disease. Participants were randomly assigned to receive 800 mg molnupiravir twice daily for 5 days plus usual care (n=12,821) or usual care only (n=12,962). Participants tracked COVID-19 outcomes via a self-completed online diary for 28 days after randomisation.

6.24 The primary endpoint was the composite of all-cause hospitalisation and death within 28 days of randomisation, and this endpoint was observed in only 0.8% of patients in both arms, indicating that in the studied group, addition of molnupiravir to usual care did not reduce the risk of the composite outcome of hospitalisation or death.

6.25 The PBAC noted that the results from the PANORAMIC trial indicated that molnupiravir did not reduce the frequency of COVID 19-associated hospitalisations or death among vaccinated adults in the community at increased risk of adverse outcomes, although results for patients aged 65 years or more trended in favour of molnupiravir (Table 7). The PBAC recalled it had considered the results from the PANORAMIC trial in November 2022[14] and recommended that an Administrative Note be added to the molnupiravir listing stating that molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable. The PBAC recalled it had previously observed that subjects in PANORAMIC were, as a whole, younger than subjects receiving molnupiravir in Australia. At that time, two-thirds of PBS utilisation of molnupiravir had been in patients ≥ 70 years of age, whereas < 15% of PANORAMIC subjects were ≥ 70 years of age. Also, it was noted that patients at highest risk of progression to severe disease in the UK were not the target population in PANORAMIC.

6.26 The PBAC noted that in contrast to the primary outcome, the results from the viral substudy of PANORAMIC reported significantly improved outcomes for participants treated with molnupiravir plus usual care compared with the usual care alone as reported by Butler et al (2023). For example, the SARS-CoV-2 viral load was undetectable on day 7 in 21% of participants in the molnupiravir plus usual care group compared with 3% in the usual care group (Adjusted OR (95% CI): 20.72 (1.12-102.23) p=0·039). The study authors noted that participants in the molnupiravir plus usual care group recovered faster than those in the usual care group, had a higher rate of early sustained recovery, and had fewer general practitioner consultations, which was consistent with a reduction in detectable virus and viral load in participants who received molnupiravir compared with those who received usual care only (Butler et al 2023, page 289).

6.27 The PBAC recalled its previous conclusion after consideration of PANORAMIC in November 2022, that while nirmatrelvir and ritonavir may be preferred for many

[14] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2022-11/covid-19-oral-treatments-outcome-nov-2022.pdf

patients with mild to moderate COVID-19 at high risk of progression to severe disease, in many common clinical circumstances nirmatrelvir and ritonavir will be contraindicated or unsuitable for use, and at that time PBAC accepted that molnupiravir remained a suitable option in such patients.

6.28 The PBAC noted that nirmatrelvir and ritonavir arm of the PANORAMIC trial is still in progress and not yet reported[15].

**Victorian linked analysis**

6.29 The submission considered that, of the studies presented, the observational study that used a linked dataset of outcomes from patients treated in Victoria, Australia was most relevant, particularly for the 70+ subgroup, at 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. The analyses were adjusted to address potential confounding due to differences in age, sex, socioeconomic status, history of hospitalisation, aged care resident status and vaccination status. Although the study did not adjust for comorbidities or concomitant medications (which were unmeasured), the adjustment for history of hospitalisation prior to COVID-19 diagnosis and aged care resident status (which are likely to some extent at least be proxies for the confounder comorbidities) was expected to partially correct for bias due to unmeasured comorbidities.

6.30 At the June ESC meeting, the ESC cautioned that the Victorian linked analysis had not yet been published and that limited information was available to assess risk of bias or study quality. The ESC noted that observational studies are typically open to bias, particularly selection bias, and substantial confounding. The ESC considered that although observational data can sometimes be used to address some of the applicability issues that may apply to the evidence from randomised controlled trials, the ESC considered that the observational data presented in the submission also had limitations. The ESC noted that the National Clinical Evidence Taskforce had reviewed the Victorian observational data but did not include analyses of these data in its evidence-to-decision framework due to the substantial risk of bias generally present in observational studies.

6.31 A pre-print manuscript for the Victorian observational study was provided to the Department after the ESC meeting and was also published on the journal's website (Van Heer 2023). The outcomes assessed were COVID-19 associated mortality and hospitalisation due to any cause within 35 days from a COVID-19 diagnosis. The analysis populations were defined as outlined below.

6.32 The analysis comparing the odds of mortality in untreated, treated with molnupiravir or treated with nirmatrelvir + ritonavir groups was based on the full cohort of patients

[15] https://www.panoramictrial.org/

(excluding only patients who died on Day 0 (i.e., same day) after diagnosis of COVID-19 and those who had previously received other antiviral medications).

6.33 The analysis comparing the odds of hospitalisation in untreated, treated with molnupiravir or treated with nirmatrelvir + ritonavir groups was based on a subgroup of the full cohort of patients. In addition to exclusion of patients who died on Day 0 (i.e., same day) after diagnosis of COVID-19 and those who had previously received other antiviral medications, patients who were hospitalised on Day 0 or Day 1 after diagnosis of COVID-19 or who resided in a Residential Aged Care Facilities (RACF) were also excluded from this analysis (on the grounds that hospital admission directives in this population do not necessarily correlate with severe disease). The PBAC noted that the risk of hospitalisation in untreated patients in the full cohort that included patients residing in RACFs (11.92%) differed substantially from the subgroup used for the hospitalisation analysis which excluded RACF patients (1.74%).

6.34 The PBAC considered that the study carried a substantial risk of bias due to its observational design. The PBAC noted concerns regarding incomplete COVID testing and reporting and differences in vaccination status. The risk of unobserved confounders may bias estimates of treatment effectiveness.

6.35 The PBAC disagreed with the pre-PBAC response which stated that the Victorian data provided a robust estimate of the effect of molnupiravir for use in the economic model. On the contrary , the PBAC considered that estimates based on the Victorian data are highly uncertain, are likely to be overly optimistic, and thus not suitable for use in the base case estimates. Notwithstanding this, the PBAC considered the Victorian data suitable to inform sensitivity analyses, and noted it was consistent with other data indicating that nirmatrelvir and ritonavir is likely more effective than molnupiravir.

**Clinical evidence for patient subgroups**

6.36 The submission, appropriately, attempted to locate evidence for the other populations beyond the 70+ subgroup and, as discussed in paragraph 6.54, attempted to consider the populations separately in the economic evaluation.

6.37 As noted by the submission, no studies specifically reported outcomes in patients with mild to moderate COVID-19 aged 50-69 with two or more risk factors for developing severe disease requiring hospitalisation. The economic analysis applied a baseline risk of hospitalisation in the 50-69 high risk cohort that was approximately one quarter of the baseline risk of hospitalisation in the 70+ cohort. The estimate was derived by taking the rates of hospitalisation by age according to the NSW Respiratory Surveillance Reports, which include benefits of treatment and do not capture risk factors, and adjusting the rates by application of a relative risk of 1.91 to adjust for increased risk in patients with risk factors (see paragraph 6.61). This approach, however, did not adjust for the benefit of treatment in the proportion of patients who were high-risk patients (but this does not bias the analysis in favour of molnupiravir). The relative risk of hospitalisation and death in the high-risk patients was derived from

a study reported by Chudasama 2021 that used data from the UK Biobank from March 2020 to July 2020 to examine the association between multimorbidity and risk of severe COVID-19.

6.38 The submission considered data from the study reported by Evans 2023 to be applicable for adults who are immunocompromised. The restriction applying for immunocompromised patients includes patients who had experienced past COVID-19 infection resulting in hospitalisation. However, this change occurred on 1 February 2023 such that the sponsor had limited time to revise the drafted submission for the March PBAC cut-off for submissions. The study reported by Evans 2023 was a retrospective analysis of electronic health records for patients in Wales testing positive for SARS-CoV-2 between December 2021 and April 2022 at high risk of hospitalisation or death due to compromised immunity.

6.39 The submission did not identify any evidence that specifically examines rates of hospitalisation and death due to COVID-19 or effectiveness of the oral antivirals in the Aboriginal and Torres Strait Islander population.

6.40 Though not a claim in the submission, a recent study of outcomes in Veterans Affairs healthcare facilities across the US, published in the British Medical Journal (Xie 2023[16]), suggests that molnupiravir use within five days of testing positive for SARS-CoV-2, compared with no treatment, was associated with reduced risk of post-acute sequelae of SARS-CoV-2 (long COVID) (RR: 0.86; 95% CI: 0.83, 0.89), reduced risk of post-acute hospitalisation (HR: 0.86; 95% CI: 0.80, 0.93) and reduced risk of post-acute death (HR: 0.62; 95% CI: 0.52, 0.74) in patients with at least one risk factor for progression to severe COVID-19.

6.41 The submission claimed that, overall, the evidence supported uncertain comparative efficacy for molnupiravir versus nirmatrelvir and ritonavir. However, the basis for this claim is, essentially, that, although point estimates generally favour nirmatrelvir and ritonavir over molnupiravir, there is a lack of statistical differences when examining results from a selection of the single retrospective cohort studies (specifically, Bajema 2022 and Yip 2022). Overall, the results presented in Table 7 indicate that both molnupiravir and nirmatrelvir and ritonavir lower the risk of hospitalisation and death, particularly in the older cohorts (who are, in general, considered to be at higher risk than younger people). Table 7 shows a consistent trend across studies toward greater reductions in risk of hospitalisation and death with nirmatrelvir and ritonavir compared to molnupiravir. Overall, the findings support the PBAC's advice that nirmatrelvir and ritonavir is preferred in a scenario where both oral antivirals are available and able to be used.

[16] Xie Y, Choi T, Al-Aly Z. Molnupiravir and risk of post-acute sequelae of COVID-19: cohort study. *BMJ.* 2023;381:e074572. https://doi.org/10.1136/bmj-2022-074572

## *Comparative harms*

6.42 Of the studies presented in the submission, only the MOVe-OUT and PANORAMIC trials assessed safety of molnupiravir.

6.43 The analysis of adverse events (AEs) in the MOVe-OUT trial indicates that molnupiravir is generally well tolerated, with 31.3% of molnupiravir-treated patients and 33.4% of placebo-treated patients experiencing adverse events (any grade). Serious adverse events were observed in 6.8% of the molnupiravir-treated group and in 9.1% of the placebo-treated group. The most frequently reported AEs (occurring in ≥ 1% of participants in either group) that were deemed to be related to the trial regimen were diarrhoea (1.7% vs. 2.1%), nausea (1.4% vs. 0.7%), and dizziness (1.0% vs. 0.7%).

6.44 Serious adverse events (SAEs) were reported for 50 (0.4%) of 12774 participants in the molnupiravir group and for 45 (0.3%) of 12934 in the usual care group in the PANORAMIC trial. None of these events were judged to be related to molnupiravir.

6.45 The submission also provided a Periodic Safety Update Report (PSUR) with reporting period from 4 May 2022 to 3 Nov 2022. Evaluation of information during the reporting period did not identify any additional clinically relevant new safety information.

6.46 The submission reported that, although the safety profiles of molnupiravir and nirmatrelvir and ritonavir are similar when considering evidence from clinical trials, the rate of serious adverse drug reactions in practice is greater with nirmatrelvir and ritonavir due to the potential for drug interactions. The submission presented an analysis of suspected drug reactions reported to the UK's Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card scheme that indicates that the rate of AEs and SAEs reported with nirmatrelvir and ritonavir is higher than with molnupiravir – SAEs: 0.79% vs 0.49% for nirmatrelvir and ritonavir and for molnupiravir, respectively. ESC considered that relative safety could not be reliably ascertained based on the available evidence.

## *Benefits/harms*

6.47 On the basis of evidence from the MOVe-OUT trial, for every 100 patients treated with molnupiravir in comparison with placebo:

- approximately 3 hospitalisations or deaths are averted within 4 weeks follow-up.

6.48 On the basis of evidence from the PANORAMIC trial, for every 100 patients treated with molnupiravir in comparison with placebo:

- no hospitalisations or deaths are averted within 4 weeks follow-up.

## *Clinical claim*

6.49 The submission described molnupiravir as superior in terms of effectiveness compared to usual care. The commentary considered this claim was adequately supported but the magnitude of the effect was uncertain. The key issue with the evidence presented was the applicability of the evidence to the Australian setting. In

addition, the observational studies were associated with a high risk of bias due to potential for differences across treatment groups in unreported or unmeasured patient characteristics. The PBAC noted that the randomised MOVe-OUT trial had demonstrated reduced hospitalisation and death with molnupiravir compared with usual care and provided the evidence for the effectiveness of molnupiravir considered by PBAC at the time of recommending the PBS listing (February 2022). However, the range of results reported in Table 7 suggested that the magnitude of the benefit is less than reported for the MOVe-OUT trial at the time of the original PBAC submission. The PBAC considered that the claim of superior effectiveness of molnupiravir compared to usual care was not robust, particularly given more recent PANORAMIC trial data.

6.50 The submission described molnupiravir as inferior in terms of safety compared to usual care but with a manageable safety profile. The PBAC considered this claim was adequately supported.

6.51 The submission claimed that, overall, the evidence supported uncertain comparative efficacy for molnupiravir versus nirmatrelvir and ritonavir. The PBAC considered that the overall body of evidence sourced from both randomised and observational trials, suggested that nirmatrelvir and ritonavir was likely more effective than molnupiravir (Table 7). The PBAC considered that the submission's claim of uncertain comparative efficacy was not adequately supported by the data, and that Table 7 showed a consistent trend across studies toward greater reductions in risk of hospitalisation and death with nirmatrelvir and ritonavir compared to molnupiravir. The PBAC maintained its previous advice that nirmatrelvir and ritonavir is preferred in a scenario where both oral antivirals are able to be used. Relative safety could not be reliably ascertained based on the available evidence.

## *Economic analysis*

6.52 The submission presented a cost-utility analysis, consistent with the claim of therapeutic superiority over usual care. Table 9 summarises the key features and key inputs to the modelled economic analysis.

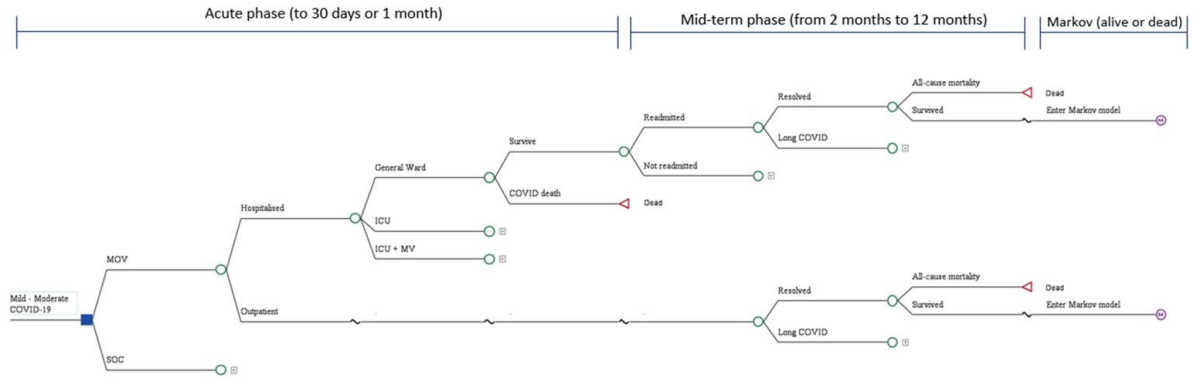
**Table 9: Summary of model structure and key inputs**

| Component | Summary |
|---|---|
| Treatments | Molnupiravir vs usual care |
| Time horizon | Lifetime time horizon |
| Outcomes | QALYs gained<br>Life years gained |
| Methods used to generate results | Year 1: decision tree analysis<br>Beyond year 1: Markov model |
| Health states | Decision tree analysis:<br>Outpatient<br>Inpatient, general ward<br>Inpatient, ICU without mechanical ventilation<br>Inpatient, ICU with mechanical ventilation<br>Hospital readmission<br>Survive without long COVID<br>Survive with long COVID<br>Markov model:<br>Alive and fully recovered<br>Dead |
| Cycle length | 30 days (month 1 of the model)<br>One month (months 2-12 of the model)<br>One year (beyond year 1 of the model) |
| Baseline rates of hospitalisation and death | 70+ subgroup and 50-69 high risk subgroup<br>Hospitalisation and death: NSW Respiratory Surveillance Reports<br><br>IC subgroup<br>Hospitalisation and death: Evans 2023 |
| Treatment effect inputs | 70+ subgroup and 50-69 high risk subgroup<br>Hospitalisation and death: preliminary Victorian DoH public data in a media release<br><br>IC subgroup<br>Hospitalisation and death: Evans 2023 |
| Health related quality of life | Goswami 2022 (de novo utility study) |

Source: Table 3.1-1, p130 of the submission.
Abbreviations: IC = immunocompromised; ICU = intensive care unit; QALY = quality-adjusted life year

6.53 The structure of the economic model is presented in Figure 4 below. The model is broken into three distinct phases: the acute phase (first 30 days after initiating treatment), the mid-term phase (from months 2 to 12) and the Markov phase (from 1 year to death). Each of the phases in the economic model capture different outcomes resulting from infection with COVID-19. The acute phase considers patient infection, hospitalisations and deaths resulting from COVID-19 and avoided by treatment with molnupiravir. The distribution of patients after the acute phase of the model has flow-on effects for the rest of the model. The mid-term phase considers risks of hospital readmissions and long COVID. There is no difference due to treatment in terms of the proportion of patients experiencing hospital readmission or long COVID after infection or hospitalisation. Lastly, the Markov phase assumes all patients surviving beyond one year to be completely recovered and the cohort follows the survival of the age-matched Australian general population to death. Background mortality is included throughout to capture deaths not due to COVID. The ESC considered that structurally, the economic model is simple yet sufficient.

**Figure 4: Structure of the economic model presented in the submission**




6.54 The economic model calculates results by three different patient populations from the PBS restriction. The populations modelled are: the 70+ subgroup, the 50-69 high risk subgroup and the IC subgroup. Following separate calculation, the results are weighted based on previous utilisation data across the populations to return a value representative of the whole cohort. In doing so, different baseline risks of hospitalisation and death and variable treatment effects are applied in the different populations. The data supporting the baseline risk and treatment effects in the 50-69 high risk and the IC subgroups have serious limitations, which leads to uncertainty in the results generated by the model. Although the approach of splitting the population into different cohorts is technically appropriate, the data for the cohorts are problematic. The PBAC has previously not considered cost-effectiveness of molnupiravir for subgroups of patients. The model presented in the rHTA was based on the MOVe-OUT results such that a single cohort was modelled.

6.55 All deaths due to COVID-19 in the model are assumed to occur only in patients that have been hospitalised, which is consistent with the approach taken in the model presented in the rHTA. Following hospitalisation, patients are separated based on the types of hospitalisation services required (general ward, ICU without mechanical ventilation and ICU with mechanical ventilation). A uniform risk of death is applied regardless of the type of hospitalisation. This is reasonable given the lack of granularity in the data source. The separation by type of hospitalisation results only in different costs and QALYs (due to quality of life) generated for the time in state. Avoiding hospitalisation therefore has a flow-on effect on deaths. Additionally, the risk of death in those hospitalised when treated with molnupiravir is lower than that in those receiving usual care. Together, these inputs result in fewer deaths in the molnupiravir arm of the economic model, which ultimately leads to QALY and survival gains compared to usual care.

6.56 Beyond the first year of the economic model, all surviving patients were considered to have fully recovered from any infection with COVID-19 and transitions are based on the survival of the age-matched Australian general population. Although the model used a Markov process to estimate survival beyond the first year, a pay-off of life-years remaining could have been applied in a decision analysis and would have given

identical results. Thus, the economic model does not capture additional benefits for patients beyond the first year of the model beyond life-years associated with deaths averted due to COVID-19. Across the three modelled populations, patients entered the Markov phase of the model at the average 'age at death' from COVID-19, which were sourced from NSW respiratory surveillance reports. Patients aged over 70 are assumed to be, on average, 86.7 years old at the time of death. Patients aged 50-69 are assumed to be, on average, 62.1 years. Patients aged 18-69 who are immunocompromised are assumed to be, on average, 59.1 years of age. Ideally, to correctly estimate life expectancy, patients who died at age 50-69 with COVID-19 in the NSW dataset should have been divided into three categories: (i) those who were immunocompromised; (ii) those who had comorbidities but were not immunocompromised; and (iii) those who did not have comorbidities and were not immunocompromised. Incorrect estimates of life expectancy will have a significant impact on the estimated cost-effectiveness of molnupiravir. If life expectancy is overestimated (e.g., if life expectancy is likely reduced in those with comorbidities compared with those without), the incremental cost-effectiveness ratio (ICER) will be underestimated.

6.57 The base case economic evaluation utilises a de novo utility evaluation study using the EQ-5D-5L published by Goswami 2022[17]. The ESC considered that the utility values were uncertain, noting that published weights from this study appeared to lack face validity. However, it was noted that the model was not sensitive to the utility values applied in the sensitivity analyses conducted in the commentary (ICERs ranged from $5,000 to < $15,000 to $5,000 to < $15,000 per QALY gained, compared with $5,000 to < $15,000 in the base case). An alternative approach for estimation of utility values could utilise the Australian EQ-5D-5L value set (Norman et al 2023)[18].

6.58 The key drivers of the economic model are presented in Table 10. The costs and outcomes generated across treatment arms are based on time in health states, with certain costs and quality of life weights applied to the different health states. By resulting in less occupancy of the more severe health states, molnupiravir reduces costs and increases QALYs accrued over time compared with usual care. The avoidance of both hospitalisations and deaths in the model due to treatment with molnupiravir leads to the incremental differences calculated by the economic evaluation, therefore, changes to these inputs are the key drivers in the cost-effectiveness estimates. The ESC noted that the inputs for baseline risk of hospitalisation and death and those for reduction in risk of these events were highly uncertain.

[17] Goswami et al. Cost-Effectiveness Analysis of Molnupiravir Versus Best Supportive Care for the Treatment of Outpatient COVID-19 in Adults in the US. Pharmacoeconomics. 2022 Jul;40(7):699-714.
[18] Norman et al. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. Pharmacoeconomics. 2023 Apr;41(4):427-438.

**Table 10: Key drivers of the model**

| Description | Method/Value | Impact on weighted base-case Base case: $[redacted][1]/QALY gained |
|---|---|---|
| Risk reduction of hospitalisation and death | The submission presented varying treatment effect of molnupiravir between populations. Changing the reduction in hospitalisation or death as a result of treatment with molnupiravir influences the QALY gains observed over the time horizon. | High<br>Decreases in the risk reductions increases the ICER |
| Baseline risk of hospitalisation and death | The baseline risks of hospitalisation and death in each of the modelled populations varies significantly. Changing the baseline risk has flow on effects for the duration of the time horizon and determines the magnitude of QALY gains. | High<br>Decreases in the baseline hospitalisation rate across populations increases the ICER |
| Time horizon | The model is sensitive to the time horizon applied. The model uses a lifetime time horizon. Over shorter time horizons, the long-term outcome of deaths averted following treatment with molnupiravir is not captured. | High, favours molnupiravir<br>Use of a one-year time horizon increased the ICER to $[redacted][2]/QALY gained. |
| Cost of molnupiravir | The submission proposed an effective dispensed price of molnupiravir of $[redacted]. This is the key driver of incremental costs between the two treatment arms of the model. | High<br>Decreases in the effective dispensed price decrease the ICER |

Source: Observations from sensitivity analyses presented in the submission and additional analyses conducted during the evaluation.
*The redacted values correspond to the following ranges:*
[1] *$5,000 to < $15,000*
[2] *$55,000 to < $75,000*

6.59 The key inputs of the economic model have been summarised in Table 11.

6.60 The submission sourced the relative risk reduction in hospitalisations and deaths in the 70+ subgroup and the 50-69 high risk subgroup attributable to molnupiravir from a press release detailing outcomes of analyses of the Victorian COVID-19 data (see Table 5). The submission assumed that the relative treatment effect of molnupiravir in 50-69 high risk subgroup would be the same as observed in the population aged 70+ receiving treatment with molnupiravir. In the absence of other reliable evidence, this is a reasonable assumption. Treatment effect (in terms of reduction in risk of hospitalisation and death) in the IC subgroup was informed by Evans 2023, a retrospective study conducted in Wales (see paragraph 6.38).

6.61 In regard to baseline risk of hospitalisation and death and given the sponsor did not have access to estimates from the analyses of the Victorian dataset, the submission used data from the NSW Respiratory Surveillance Reports to estimate the proportion of patients with COVID-19 who are hospitalised and who die. The submission assumed that all patients that died in the NSW Respiratory Surveillance Reports died in hospital (consistent with the assumption in the economic model). As noted by the submission, the proportion of patients in each age group who are hospitalised and who have died with COVID-19 as reported by the NSW Respiratory Surveillance Reports incorporate patients who are treated with antivirals and do not differentiate patients with risk factors from those that do not have risk factors.

6.62 For the population aged ≥ 70 years, baseline risk of hospitalisation and death is derived from rates reported for this population in the NSW Respiratory Surveillance Reports. The submission acknowledged that the rates reported include the impact of treatment

and it therefore made adjustments to the observed rates to remove the impact of treatment.

6.63 For patients in the 50-69 year age group, the submission applies a multiplier to adjust the estimates so as to capture the impact of multiple risk factors in the PBS population. However, no adjustments are made to adjust for benefits of treatment that will also be reflected in the risks of hospitalisation and death reported by the NSW Respiratory Surveillance reports.

6.64 For the immunocompromised population, the submission applied the risk of hospitalisation or death observed in untreated patients in the study reported by Evans 2023 to estimate the proportion of patients hospitalised in the usual care arm (a reasonable implicit assumption is made that the deaths in this study occurred in hospitalised patients). In the absence of specific data for deaths, the submission assumed the same proportion of hospitalised patients in the IC subgroup die as observed in the NSW raw 70+ subgroup data (i.e., without removing the impact of treatment).

6.65 In summary, due to the lack of available relevant data, the submission combined available data from multiple sources, necessitating various assumptions to align the available data with the model's parameters. This resulted in compounding of uncertainty in the generation of results by the economic model. Ultimately, as shown in Table 11, the submission assumed that the three modelled populations have vastly different risks hospitalisation and death rates at baseline. Given the variation in the values assumed for these parameters across the different populations, estimates of cost-effectiveness in each of the three populations are also markedly different. The ESC noted that although it was theoretically appropriate to split the subgroups in the model, the data used to populate the subgroups were inadequate to be able to do this in a robust way and therefore the results generated by the model are highly uncertain.

**Table 11:Key inputs applied in the economic model**

| Key transition probabilities and risk reductions in the economic model | 70+ | 50-69 high risk | 18-69 IC |
|---|---|---|---|
| **All patients hospitalised** | | | |
| Risk of hospitalisation in patients managed with usual care | 6.41% | 1.77% | 10.90% |
| RR hospitalisation in molnupiravir-treated patients | 0.74 | 0.74 | 0.65 |
| Risk of hospitalisation in molnupiravir-treated patients | 4.74% | 1.31% | 7.09% |
| **Proportion of hospitalised patients dying** | | | |
| Risk of death in hospitalised patients treated with usual care | 30.90% | 7.18% | 27.98% |
| RR death in molnupiravir-treated patients | 0.46 | 0.46 | 0.65 |
| Risk of death in hospitalised patients treated with molnupiravir | 14.22% | 3.30% | 18.19% |

Abbreviations: IC = immunocompromised; RR = risk reduction

6.66 The submission presented results of the economic evaluation by treatment phase and by subgroup. As can be seen from Table 12, the ICER decreased as the time horizon examined by the economic model was extended from one phase to the next for each of the modelled subgroups. This is primarily due to the capture of years of life saved from averted deaths. There was a substantial difference in the ICER generated for each subgroup as can be seen from Table 12. The submission included supplementary analyses that took a societal perspective, where productivity losses and hospital opportunity cost losses (e.g., due to having to reduce elective services) due to COVID-19 were considered (see Table 12).

**Table 12: Results of the economic evaluation by treatment phase and population**

| Step and component | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| **Total weighted population** | | | |
| Acute phase (30 days) | $ | 0.0007 | $ [1] |
| Mid-term phase (1 year) | $ | 0.0098 | $ [2] |
| Markov phase (lifetime) | $ | 0.0870 | $ [3] |
| Societal perspective | $ | 0.0870 | $ [4] |
| **70+ subgroup** | | | |
| Acute phase (30 days) | $ | 0.0008 | $ [1] |
| Mid-term phase (1 year) | $ | 0.0108 | $ [2] |
| Markov phase (lifetime) | $ | 0.0646 | $ [3] |
| Societal perspective | $ | 0.0646 | $ [3] |
| **50-69 high risk subgroup** | | | |
| Acute phase (30 days) | $ | 0.0001 | $ [5] |
| Mid-term phase (1 year) | $ | 0.0008 | $ [6] |
| Markov phase (lifetime) | $ | 0.0103 | $ [7] |
| Societal perspective | $ | 0.0103 | $ [2] |
| **IC subgroup** | | | |
| Acute phase (30 days) | $ | 0.0011 | $ [8] |
| Mid-term phase (1 year) | $ | 0.0153 | $ [9] |
| Markov phase (lifetime) | $ | 0.2269 | $ [4] |
| Societal perspective | -$ | 0.2269 | **DOMINANT** |

Source: Table 3.8-1, p185 of the submission.

*The redacted values correspond to the following ranges:*

[1] *$855,000 to < $955,000*
[2] *$55,000 to < $75,000*
[3] *$5,000 to < $15,000*
[4] *$0 to < $5,000*
[5] *> $1,055,000*
[6] *$955,000 to < $1,055,000*
[7] *$75,000 to < $95,000*
[8] *$255,000 to < $355,000*
[9] *$15,000 to < $25,000*

6.67 Table 13 presents the results of the base case economic evaluation excluding indirect costs (e.g., due to productivity gains). Following weighting of the cost-effectiveness for each subgroup, the economic model estimates an ICER of $5,000 to < $15,000 per QALY gained. As discussed previously, there is wide variation in the ICERs generated for each of the subgroups, ranging from $0 to < $5,000 per QALY gained in the IC subgroup to $75,000 to < $95,000 per QALY gained in the 50-69 high risk subgroup. The largest group in the utilisation estimates was the 70+ subgroup, comprising 60.7%

of antiviral prescriptions on the PBS from August 2022 to December 2022, therefore the cost-effectiveness of this group has the largest influence on the weighted results.

**Table 13: Results of the economic evaluation**

| Component | Molnupiravir | Usual care | Increment |
|---|---|---|---|
| Drug costs | $ | $ | $ |
| Outpatient costs | $96.47 | $94.58 | $1.89 |
| Hospital costs | $776.89 | $1,105.00 | -$328.11 |
| **Total costs** | **$** | **$** | **$** |
| **QALYs** | **7.8497** | **7.7627** | **0.0870** |
| **LYs** | **9.2346** | **9.1326** | **0.1020** |
| **Incremental cost per QALY gained (weighted population)** | | | **$** [1] |
| **Incremental cost per LY gained (weighted population)** | | | **$** [1] |
| Incremental cost per QALY gained (70+ subgroup) – submission base case | | | $ [1] |
| Incremental cost per QALY gained (50-69 high risk subgroup) | | | $ [2] |
| Incremental cost per QALY gained (IC subgroup) | | | $ [3] |
| Pre-PBAC response | | | |
| Incremental cost per QALY gained (70+ subgroup) – Pre-PBAC response* | | | $ [3] |

* Uses updated inputs from manuscript as shown in Table 15.
Source: Table 3.8-2, p186 of the submission.
Abbreviations: IC = immunocompromised; LY = life year; QALY = quality-adjusted life year.
*The redacted values correspond to the following ranges:*
[1] *$5,000 to < $15,000*
[2] *$75,000 to < $95,000*
[3] *$0 to < $5,000*

6.68 The submission estimated hospital costs using National Hospital Cost Data Collection (NHCDC) data. The AR-DRG codes used were: E41B (Respiratory System Disorders W Non-Invasive Ventilation, Minor Complexity), E41A (Respiratory System Disorders W Non-Invasive Ventilation, Major Complexity) and E40A (Respiratory System Disorders W Ventilator Support, Major Complexity). The ESC considered this was appropriate given that specific estimates for COVID related admissions based on age and gender had not been published.

6.69 The results of key sensitivity analyses are summarised in Table 14. The results of the model are relatively robust and the weighted ICER remains < $15,000 to < $25,000/ per QALY in all scenarios. The key drivers of the ICER are: cost per course of treatment, baseline risk of hospitalisation, baseline risk of death and treatment effect of molnupiravir.

**Table 14: Sensitivity analyses**

| Analyses | Incremental cost ($) | Incremental QALY | ICER | % change to ICER |
|---|---|---|---|---|
| **Base case** | [redacted] | **0.0870** | $[redacted] [1] | |
| Cost per course of treatment with molnupiravir (base case = $[redacted]) | | | | |
| Halve the cost of molnupiravir ($[redacted]) | [redacted] | 0.0870 | $[redacted] [2] | -76% |
| Double the cost of molnupiravir ($[redacted]) | [redacted] | 0.0870 | $[redacted] [3] | +152% |
| Baseline risk of hospitalisation or death (base case = see Table 11) | | | | |
| Assume the same baseline risks of hospitalisation and death as the 70+ subgroup for the 50-69 high risk subgroup | [redacted] | 0.1153 | $[redacted] [1] | -29% |
| Treatment effect (base case = see Table 11) | | | | |
| Assume the same treatment effect for all subgroups using the published Victorian data | [redacted] | 0.0934 | $[redacted] [1] | -2% |
| Multivariate analyses | | | | |
| Assume all subjects have the same baseline risk of hospitalisation of 6.41% and a RR of 0.74 in molnupiravir-treated patients AND a baseline risk of death of 1.98% and RR of 0.46 molnupiravir-treated patients, based on the data used in the 70+ subgroup | [redacted] | 0.1033 | $[redacted] [1] | -10% |

Source: Additional analyses conducted during the evaluation.
Abbreviations: QALY = quality adjusted life year; RR = risk reduction.
*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 ESC noted that limited validation of the economic model was conducted by the submission. Cohort disposition at the end of 12 months for each treatment arm was presented in the submission to demonstrate the model correctly applied clinical inputs, and the logic and calculations were verified during the evaluation. The ESC considered that further validation of the modelled traces against published studies would be informative when further clinical data become available.

6.71 The pre-PBAC response stated that the cost effectiveness of molnupiravir improved after inclusion of the inputs from the pre-print manuscript (Van Heer et al. 2023), and stated that the price offered accounted for any uncertainty within the data. The results of the economic model for the 70+ population based on the published data are provided in Table 15. The ICER in the 70+ group reduced from $5,000 to < $15,000 to $0 to < $5,000 per QALY gained. The response stated this was due to higher baseline rates of hospitalisation and deaths reported in the publication relative to what was assumed in the economic model and to slightly greater treatment effects reported in the publication relative to the online article available to the sponsor at the time of submission (Table 15).

**Table 15: Economic model inputs and results in the 70+ population**

| 70+ population | Updated model inputs | Submission model inputs |
|---|---|---|
| Hosp rate (SOC) | 11.90% [a] | 6.41% |
| ICU rate (SOC) | 0.89% [b] | 0.48% |
| Death rate (SOC) | 3.40% [a] | 1.98% |
| Age of COVID-affected population | 77.0 [c] | 79.5 |
| Relative reduction in hospitalisation with MOV | 0.29 [d] | 0.26 |
| Relative reduction in death with MOV | 0.55 [d] | 0.54 |
| ICER | $[redacted] [1] | $[redacted] [2] |

a. Updated hospitalisation and deaths rates for the SOC arm based on Table 1 (Cowie, 2023)
b. ICU rates not reported in Cowie. Updated assuming the ratio of ICU:hospitalisation as per the submitted model (0.89=0.48/6.41*11.90)
c. Table 1 (Cowie, 2023)
d. Relative reductions from Cowie (2023) reported and applied as odds ratios (as opposed to relative risk reduction in the submitted model inputs)
Source: Pre-PBAC response addendum. Results have not been independently verified.
*The redacted values correspond to the following ranges:*
*[1] $0 to < $5,000*
*[2] $5,000 to < $15,000*

6.72 The submission also presented a cost-minimisation analysis comparing molnupiravir to nirmatrelvir and ritonavir that assumes therapeutic non-inferiority of molnupiravir compared to nirmatrelvir and ritonavir. The submission claimed there was insufficient evidence to determine one treatment was superior to the other. However, as discussed in paragraphs 6.41 and 6.51 the assumption of non-inferior effectiveness does not appear to be supported by the totality of the available evidence.

6.73 Regardless of whether nirmatrelvir and ritonavir is an appropriate comparator, the commentary considered it could be reasonable for nirmatrelvir and ritonavir to provide a frame of reference for judging the cost-effectiveness of molnupiravir given the objective of treatment with nirmatrelvir and ritonavir is identical to the objective of treatment with molnupiravir i.e., avoidance of hospitalisation and death. The dispensed price per course of nirmatrelvir and ritonavir is $1,113.99 for the standard 5-day course of treatment.

**Expectation of value for money at the time of listing of molnupiravir on the PBS**

6.74 The modelled economic analysis presented in the rHTA assumed a baseline risk of hospitalisation of 19.1% in patients with mild to moderate COVID-19 at high risk of developing severe disease requiring hospitalisation in the base case. A relative risk of 0.696 was applied in the economic analysis such that 5.81 hospitalisations were expected to be avoided per 100 patients treated with molnupiravir. Thus, the incremental cost of molnupiravir (based on the current dispensed price) per hospitalisation averted was $18,968 ($1,101.30/0.0581). Notably, this estimate was associated with a high degree of uncertainty (e.g., due to uncertainty around the baseline risk of hospitalisation, due to uncertainty about benefits at various stages of each wave of infection [e.g., interventions used at the peak of a wave could prevent overcrowding of the hospital system], uncertainty around impact on mortality, etc) and thus a wide confidence interval should be applied around this estimate. The pre-PBAC response noted that while the base case for the rHTA assessment assumed a baseline risk of hospitalisation of 19.1%, the PBAC consideration in February 2022

had also considered a sensitivity analysis which assumed 6.6% for this input, reflecting the baseline risk of hospitalisation in a vaccinated population and resulting in an ICER of $35,000 to < $45,000/QALY.

**Overall assessment**

6.75 The PSCR noted that the evaluation commented on the opportunity cost of oral antivirals to the PBS and stated this should be balanced against the wider opportunity cost of not treating COVID-19 and resulting impacts on the healthcare system and society. The PSCR stated that the ICER remains the best measure of the respective trade-offs, where an ICER of less than $10,000 strikes that balance and is in-line with that previously accepted for similar treatments (ledipasvir/sofosbuvir for Hepatitis C <$15,000/QALY)[19]. The PBAC did not accept that treatment of hepatitis C was a sufficiently similar clinical context to treatment of COVID-19 for ICER comparisons to be informative, including among other differences that hepatitis C antiviral treatments are curing a chronic condition that causes long term morbidity and deaths from liver disease and cancer.

6.76 Given the purpose of the submission was to present the PBAC with evidence to inform a review of its decision to recommend molnupiravir for inclusion on the PBS for patients with COVID 19 at high risk of hospitalisation, the ESC disagreed with the view expressed in the PSCR that the decision on whether molnupiravir 'is cost-effective should be based on its current economic performance, not on a historic precedent'.

6.77 The ESC considered that the PBAC's intent for the review was to ascertain whether performance (including cost-effectiveness) of molnupiravir in practice has been consistent with expectations at the time of recommendation. The ESC noted the limitations of data available to inform the cost-effectiveness assessment of the patient subgroups.

## *Molnupiravir cost/patient/course*

6.78 One pack of molnupiravir as listed on the PBS provides sufficient treatment for the standard 5-day course of treatment. The proposed effective dispensed price per course is $[redacted] (AEMP= $[redacted]), which is a reduction from the current price for one pack of molnupiravir (DPMQ = $1,101.39; AEMP=$988).

## *Estimated PBS usage & financial implications*

6.79 This submission was considered by DUSC.

6.80 The submission estimated utilisation and associated financial implications based on an epidemiological approach in addition to an approach based on utilisation of oral antivirals from July to December 2022 on the PBS. Ultimately, the submission used the market-based approach to estimate utilisation. This approach generated higher

[19] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/ledipasvir-sofosbuvir-psd-march-2015.pdf

estimates of utilisation than the epidemiological approach. Table 16 summarises the inputs to the financial analyses and the sources for those inputs.

**Table 16: Key inputs for financial estimates**

| Parameter | Value applied and source | Comment |
|---|---|---|
| Incident population diagnosed with COVID-19 | Assumption of 4 waves of COVID-19 per year, each with a median duration of 14 weeks. The peak of each wave is assumed to occur at 7 weeks and it is assumed the amplitude of the wave is 3.65 times the pre-wave case numbers. The source of these estimates is modelling of COVID-19 cases in 15 countries as reported by the WHO. | Potentially overestimated – if utilisation of the oral antivirals is correlated with number of cases of COVID-19 in the community, then Figure 1 suggests that Australia experienced 2 major waves over this period. The validity of the assumption of 4 waves per year every year is uncertain and results in a high utilisation estimate per year (56 weeks; 4 waves x 14 weeks). The assumption that the peak of the wave is approximately 3.65 times the pre-wave case numbers appears to be reasonable. DUSC agreed with the commentary that this parameter was overestimated. DUSC considered whether modelling based on influenza could be used. |
| Proportion dispensed oral antivirals | Assumption - 18% of all patients diagnosed with COVID-19 would be dispensed an oral antiviral. The source of this estimate is derived based on utilisation of oral antivirals between July 2022 and September 2022. July 2022 was selected because availability of the antivirals was expanded at this time and September 2022 was selected as the end of the period because it was the last month of mandatory reporting of COVID-19. | Potentially overestimated. As noted by the submission, the actual proportion of cases dispensed an oral antiviral over this period was 14%. The submission increases this estimate to 18% (i.e., a 28.6% increase on the observed estimate) on the basis of GP and patient familiarity with antivirals and impact of campaigns on the availability of antivirals. DUSC agreed with the commentary. |
| Market share | Molnupiravir is assumed to capture [redacted]% of the oral antiviral market. | DUSC considered this assumption would be overestimated if treatment guidelines are followed, as contraindicated medicines can be withheld during treatment with nirmatrelvir and ritonavir. DUSC considered other administrative changes could be attributed to the change in market share. DUSC noted in February 2023, the PBS listing of nirmatrelvir and ritonavir was extended to include patients aged 60-69 years with mild to moderate COVID-19 and one additional risk factor until Commonwealth purchased stock is exhausted or has expired. Additionally, DUSC noted utilisation data to be immature in a dynamic disease market. |

| Parameter | Value applied and source | Comment |
|---|---|---|
| Supply for Prescriber bags | The submission assumes the prescriptions for molnupiravir for prescriber bags will represent 2.9% of all prescriptions for molnupiravir in each of the forward years. The source for this estimate is the split of prescriptions from November and December 2022 (given that molnupiravir has only been able to be prescribed for inclusion in prescriber bags since November 2022). | This may be an over-estimate as the proposed percentage may include initial uptake to stock prescriber's bags, rather than treating presenting patients. This will diminish to a level which is replacement of used/expired units in the future. |
| PBS utilisation approach | The submission assumes utilisation of oral antivirals, as observed from July 2022 (where the restrictions for access to the antivirals was expanded) through to December 2022 could be a basis for estimating utilisation in the future. It was assumed that utilisation will be double the observed utilisation observed over these six months. In addition, population growth at 1.3%, consistent with ABS statistics is applied. | Likely overestimated. As can be seen from Figure 1, most of the period between July and December 2022, Australia was in the peak of a wave of COVID-19.<br><br>DUSC noted the population growth assumption of 1.3% is based on the total general population and commented that this figure was likely underestimated as molnupiravir would likely be used in older patients. |

Abbreviations: WHO = World Health Organization
Source: Section 4.2 of the submission

6.81 Table 17 summarises the estimated extent of use of molnupiravir from 2024 to 2029 (inclusive) and the associated financial implications. For reference, the number of PBS/RPBS prescriptions dispensed for molnupiravir in the year ending 31 March 2023 was 502,858 and total expenditure on molnupiravir over the same period was approximately $564 million. For the majority of this time, no administrative note suggesting that molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable was in place (the administrative note was added in January 2023). However, the restrictions applying through to July 2022 were also more stringent than the current restrictions. Although it is acknowledged that it is difficult to predict utilisation of oral antivirals in the future, the estimates projected by the submission are likely to be overestimates.

**Table 17: Estimated use and financial implications based on the proposed effective price**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | | |
| Number of PBS/RPBS prescriptions | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| Number of prescriber bag prescriptions | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| **Estimated financial implications of molnupiravir** | | | | | | |
| Net cost to PBS/RPBS (i.e., less copayments) | $[redacted][3] | $[redacted][3] | $[redacted][3] | $[redacted][3] | $[redacted][3] | $[redacted][3] |

Source: Tables 4.2-4 and 4.4-1 of the submission.
*The redacted values correspond to the following ranges:*
*[1] 600,000 to < 700,000*
*[2] 10,000 to < 20,000*
*[3] $600 million to < $700 million*

6.82 The total cost to the PBS/RPBS of listing molnupiravir was estimated to be $600 million to < $700 million in 2029 (Year 6), and a total of > $1 billion in the next

6 years of listing (from 2024 to 2029). As noted in Table 16, the submission assumed % market share for molnupiravir.

6.83 In the year ending 31 March 2023, total government expenditure on antivirals for COVID-19, based on items processed, totalled $798 million. Total government expenditure based on all PBS/RPBS items processed was $16,113 million. Thus, expenditure on oral antivirals represented approximately 5% of total spending on the PBS (before rebates). 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.

6.84 The DUSC considered that submission's approach of estimating future use of molnupiravir based on six months of data from July to December 2022, where the two waves of COVID 19 occurred, was likely to result in an overestimate of likely extent of use in the future. Furthermore, the approach did not adjust for the addition of the administrative note in January 2023 which states that molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable. The DUSC considered market share of molnupiravir was likely overestimated.

6.85 The pre-PBAC response stated that whilst it is not possible to accurately predict the future of the pandemic, actual utilisation data from Jan-23 to Jun-23 indicates that a minimum 600,000 units of oral antivirals would be required with up to approximately 1 million doses should future waves mirror utilisation between Jul-22 to Dec-22. The sponsor noted the comments regarding the molnupiravir market share and stated that the current share appropriately reflects the complex patient population that the PBS listing is for.

## *Quality Use of Medicines*

6.86 The submission states that antiviral treatments are an important tool for protecting vulnerable Australians against the development of severe COVID-19 disease. MSD indicates that it will focus on the following quality use of medicine objectives:

- Keeping prescribers up to date with clinical data and oral antiviral (OAV) reimbursement criteria
- Encouragement of high-risk patients to seek early medical advice should they contract COVID-19
- Continued education of prescribers, pharmacists and patients to ensure they are aware of risks of development of resistance to antivirals and how best to mitigate against these risks by reducing inappropriate use

### *Financial Management – Risk Sharing Arrangements*

6.87 The pre-PBAC response indicated a willingness to work collaboratively with the Department to ensure a suitable Risk Sharing Agreement (RSA) structure can be developed that balances security of supply, appropriate use, and managed distribution.

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

## 7 PBAC Outcome

7.1 The PBAC provided advice regarding molnupiravir for the treatment of patients with mild to moderate Coronavirus disease (COVID-19) who are at high risk of developing severe disease requiring hospitalisation. The PBAC advised that the sponsor's submission did not adequately support continuation of the current PBS listing of molnupiravir, and that additional information is required to inform further consideration of this matter. The PBAC noted the continued toll of the pandemic and the disproportionate effects on older Australians despite vaccination, and the preference expressed by consumers, clinicians and public health experts to maintain molnupiravir on the PBS as an option for patients who could not use nirmatrelvir and ritonavir (Paxlovid). The PBAC considered all available evidence on the effectiveness and safety of molnupiravir including the randomised trials MOVe OUT and PANORAMIC and noted that the effectiveness in trials as measured by reductions in hospital admissions and mortality ranged between no effect and a modest benefit. The PBAC noted that observational trials showed results consistent with modest benefits, noting that the observational trials were subject to a range of biases. The PBAC considered that the cost-effectiveness of molnupiravir was highly uncertain due to the uncertainty of effectiveness. The PBAC noted that the estimated utilisation and therefore financial impact appeared to be very high relative to the current use (and given PBAC preference that this drug only be used where the more effective treatment (nirmatrelvir and ritonavir) is not suitable). Further clarification was also needed in the restriction regarding the limited patient groups where molnupiravir should be used. The PBAC noted that the current PBS listing would be maintained pending further consideration.

7.2 The PBAC recalled its previous advice in November 2022, that the preferred anti-viral based on clinical trial data was nirmatrelvir and ritonavir and that more recent publications of indirect comparisons supported the role of nirmatrelvir/ritonavir over molnupiravir. Furthermore, PBAC considered that while there had been an increase in the relative use of nirmatrelvir and ritonavir compared to molnupiravir, further efforts are required to promote the use of the more effective agent and limit use of the lesser effective agent to situations where nirmatrelvir and ritonavir was absolutely contra-indicated.

7.3 The PBAC considered there was a lack of clarity on the clinical place for molnupiravir, given that utilisation data showing majority market share for molnupiravir compared

with nirmatrelvir and ritonavir did not reflect clinical guidelines. The PBAC noted that molnupiravir is no longer recommended for routine use in Australia (paragraph 5.9).

7.4 The PBAC noted the preference expressed by consumers, clinicians and public health experts to maintain molnupiravir on the PBS as an option for patients who could not use nirmatrelvir and ritonavir.

7.5 The PBAC noted that since the initial PBAC consideration of molnupiravir in February 2022, one large, randomised study of molnupiravir has been published (PANORAMIC), which was considered by the PBAC in November 2022; the study was not considered fully generalisable to the PBS population.

7.6 The PBAC noted that a pre-print manuscript for the Victorian dataset was available, however considered that the study carried a substantial risk of bias due to its observational design (paragraph 6.35).

7.7 Based on the usual preference of PBAC for effectiveness to be based on randomised clinical trials the PBAC considered that molnupiravir would not be cost-effective at the requested price in light of the clinical effectiveness reported in the PANORAMIC data.

7.8 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. The PBAC considered that the claim of uncertain comparative efficacy was not adequately supported by the submission, and relative safety could not be reliably ascertained based on the available evidence.

7.9 The PBAC considered that the cost-effectiveness of molnupiravir was highly uncertain due to the uncertainty of effectiveness. The PBAC noted that the wide variation in ICERs generated for each of the subgroups presented in the submission, ranging from \$0 to < \$5,000 per QALY gained in the IC subgroup to \$75,000 to < \$95,000 per QALY gained in the 50-69 high risk subgroup (Table 13). The largest group in the utilisation estimates was the 70+ subgroup, comprising 60.7% of antiviral prescriptions on the PBS from August 2022 to December 2022, therefore the cost-effectiveness of this group has the largest influence on the weighted results. The PBAC agreed with the ESC that it was theoretically appropriate to split the subgroups in the model, however the data used to populate the subgroups were inadequate to be able to do this in a robust way and therefore the results generated by the model were highly uncertain. The PBAC noted that none of the evidence presented for molnupiravir was specific to patients with absolute contraindications to nirmatrelvir and ritonavir.

7.10 Based on the available clinical evidence, the PBAC considered that a substantial reduction in price would be required to support continued listing. The rationale for the requested price reduction was to overcome the uncertainty in cost-effectiveness arising from, in the main, uncertain extent of clinical benefit in the target populations. The PBAC noted that several publications reported significantly improved effectiveness with nirmatrelvir and ritonavir, compared with molnupiravir (Table 7).

7.11 The PBAC noted that the estimated utilisation and therefore financial impact

appeared to be very high relative to the current use (and PBAC anticipated utilisation patterns with increased relative use of the more effective agent). The PBAC considered that the estimates should be revised to account for the concerns raised in Table 16. Given uncertainty of the estimates, it may be appropriate to consider a Risk Sharing Arrangement for a three-year period rather than the usual six-year period.

7.12 The PBAC provided the following comments on the restriction:

- The PBAC considered that the administrative note should be formalised in the restriction as a separate clinical criterion to provide greater clarity to prescribers on the appropriate population for molnupiravir.
- An increase to the restriction level for molnupiravir may be considered, although the PBAC noted that it did not want administrative requirements to delay treatment initiation. The PBAC also acknowledged that substantial work had been undertaken to promote early use of antiviral therapy as a component of Australia's pandemic response. The PBAC noted that greater adherence was required regarding the NCET guidance that molnupiravir is no longer recommended for routine use in Australia.
- Further clarification was needed to determine whether the prescriber bag listing was still fit for purpose.

7.13 The PBAC considered that a substantial price reduction for molnupiravir would be required, noting that the sponsor's submission did not adequately support that the current PBS listing is cost-effective. The PBAC noted the reduced AEMP offered by the submission of $ for 40 capsules, as compared with the current AEMP of $988. The PBAC considered that the offered reduction was insufficient to address the uncertainties regarding the effectiveness and cost-effectiveness, however advised it would be appropriate for the sponsor's proposed reduced price to be implemented in the interim, while additional information is sought to inform further consideration of this matter.

7.14 The PBAC considered that the issues described in these minutes would require a resubmission for molnupiravir and requested that the sponsor lodge the resubmission for consideration at the November 2023 PBAC meeting if possible, no later than 13 September 2023. The following changes may address the outstanding issues:

- Restriction: clarification of the appropriate population (see paragraph 7.12).
- Cost-effectiveness: a substantial reduction in price to support continued listing (see paragraph 7.10) in a population ineligible for nirmatrelvir and ritonavir.
- Recalculation of the financial implications using revised inputs as discussed in paragraph 7.11 and revised price.

7.15 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 at the time. The

PBAC recognised the challenges that changes to the evidence base, and clinical guidance, have produced in that context. The PBAC considered that it was preferable for issues for the ongoing PBS listing of molnupiravir, if any, to be resolved as expeditiously as possible. Noting this, and the tight timeframe for re-consideration by PBAC in the 2023 calendar year (as outlined in paragraph 7.14), the PBAC asked the Department to work closely with the sponsor to consider any options that may assist PBAC reconsideration in a timely manner.

7.16 The PBAC noted that this submission is not eligible for an Independent Review as it was not seeking an additional indication for molnupiravir on the PBS.

**Outcome:**
Advice Provided

# 8 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.

# 9 Sponsor's Comment

MSD is disappointed that PBAC preferred the randomised clinical trials and considered that the observational data had substantial risk of bias. MSD will endeavour to work with the PBAC to ensure molnupiravir continues to be available for vulnerable COVID - positive patients who are unable to take other antivirals.

**Addendum to the July 2023 PBAC Public Summary Document (PSD)**

# 4.04 MOLNUPIRAVIR, Capsule 200 mg, Lagevrio®, Merck Sharp & Dohme (Australia) Pty Ltd.

## 10 Purpose of submission

10.1 The submission was lodged to address issues raised by the PBAC in its consideration of molnupiravir at the July 2023 meeting.

## 11 Background

### *Registration status*

11.1 Molnupiravir was granted provisional approval by the TGA on 20 January 2022 for 'the treatment of adults with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk for hospitalisation or death'. Provisional approval was granted for a two-year period, with the consent to import or supply molnupiravir effective until 18 January 2024. On 1 September 2023, the TGA granted a 2-year extension to the provisional registration of molnupiravir, to 18 January 2026.

11.2 Additional information was requested from the sponsor regarding molnupiravir in other jurisdictions. A summary of overseas registration status was provided as shown in Table 18. The correspondence stated that reimbursement status varies depending on the funding arrangements for oral antivirals (OAVs; whether in stockpile or on general schedule) and the patient population reimbursed, which varies across jurisdictions, and that utilisation metrics are not available to the local sponsor with respect to use of molnupiravir in other countries. The PBAC noted that no status was provided for the EMA, however the sponsor had previously notified the Department of the withdrawal of the EU application for marketing authorisation of molnupiravir (see paragraph 2.3).

**Table 18: Overseas registration status for molnupiravir 200 mg capsules as of 21 June 2023**

| Country/Region | Authorisation/Approval | Date |
|---|---|---|
| UK | Conditional Marketing Authorisation (CMA) | 04 Nov 2021 |
| US | Emergency Use Authorisation | 23 Dec 2021 |
| Japan | Approval with conditions<br>Conditions fulfilled | 24 Dec 2021<br>24 Apr 2023 |
| Malaysia | Conditional Approval | 07 Apr 2022 |
| New Zealand | Provisional Consent | 14 Apr 2022 |
| China | Drug Marketing Registration - Conditional Approval | 29 Dec 2022 |
| South Africa | Marketing Authorisation | 06 Dec 2022 |
| Colombia, Dominican Republic, Hong Kong, Kuwait, Mexico, Oman, Panama, Peru, Saudi Arabia, South Korea, Taiwan, Thailand, Ukraine, United Arab Emirates | Emergency Use Authorisation | Multiple dates (Dec 2021 through Jan 2023) |

Source: Provided by sponsor via correspondence to Department on 3 Oct 2023.

# 12 Requested listing

## *Clarification of the appropriate population*

12.1 The submission stated that retention of the current molnupiravir listing is required to ensure equity of access to oral antivirals (OAVs), given that some vulnerable patients are contraindicated or otherwise unsuitable for nirmatrelvir and ritonavir. The pre-PBAC response stated that molnupiravir continues to be an important tool to protect vulnerable Australians from severe COVID-19, especially in light of recent data indicating only 53% of those aged ≥65 years have been vaccinated for COVID-19 in the last 6 months[20].

12.2 The wording of the PBS restrictions proposed by the sponsor was consistent with the July 2023 submission as set out in Section 3 above, except that the submission proposed that the administrative note be converted to a clinical criterion stating: 'This drug should be considered for use only if nirmatrelvir (&) ritonavir is contraindicated or otherwise unsuitable'. The ESC noted that the absence of a definition for the phrase 'contraindicated or otherwise unsuitable' leaves this restriction criterion open to a broad range of interpretations. The pre-PBAC response suggested that although the restriction is 'open to interpretation', this is necessary to ensure appropriate clinical decision making by the treating clinician.

12.3 The submission stated that clinical considerations extend beyond whether a patient is on a drug where concomitant use with nirmatrelvir and ritonavir is contraindicated. It was noted that clinician feedback indicated complexity and diversity of clinical presentations to GPs. Other stated reasons for prescribing molnupiravir included 1) safety concerns with cessation or dose titration of existing medications; 2) specialist advice that existing medications should not be stopped; 3) patient cognition issues

[20] 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.

which may impact ability to safely execute prescribed changes to concomitant medications; and 4) lack of patient consent to stop or alter existing medications. The submission stated that many elderly patients presenting to GPs are multi-morbid, on numerous medications, with additional considerations such as frailty, and poor cognitive status, and it is 'overly simplistic' to consider medication changes straightforward for vulnerable patients presenting with COVID-19.

12.4 Consistent with previous PBAC advice, the ESC considered that molnupiravir is not as effective as nirmatrelvir and ritonavir, however there are a subset of people who cannot receive the latter. The ESC considered there is a role for molnupiravir in patients at high risk but cannot receive nirmatrelvir and ritonavir. The ESC noted that remdesivir is another alternative but as it is administered intravenously it is given in a hospital setting. The ESC noted that NCET guidelines[21] state 'The efficacy of remdesivir in vaccinated adults and immunocompromised patients is unknown'.

12.5 The submission indicated that the Prescriber Bag item number for molnupiravir may no longer be necessary and did not raise any objections to removal of molnupiravir prescriber bag code from the PBS.

## *Proposed price*

12.6 The submission requested no change to the published price per pack (DPMQ: $1,102.24; AEMP: $988).

12.7 The submission proposed tiered pricing for molnupiravir based on utilisation of all oral antivirals under a risk-sharing agreement (RSA) as shown in Table 19. The submission stated that the price volume tiers (Table 19) are 'contingent on acceptance of the proposed restriction, no volume or expenditure cap and OAV usage in high risk patients with mild to moderate COVID-19, not lower risk patients that MOV is not PBS listed for'.

12.8 The effective approved ex-manufacturer price (AEMP) proposed in the submission, under a special pricing arrangement (SPA) was $ | (based on estimates of average effective ex-manufacturer price over 3 years).

**Table 19: Proposed molnupiravir price tiers based on utilisation of oral antivirals**

| Utilisation of oral antivirals | Proposed molnupiravir effective ex-manufacturer price | | Effective DPMQ in submission | | Corrected effective DPMQ | |
|---|---|---|---|---|---|---|
| 0 – 200,000 | | | | | | |
| 200,001 -400,000 | | | | | | |
| 400,001 – 600,000 | | | | | | |
| 600,001 – 800,000 | | | | | | |
| > 800,001 | | | | | | |

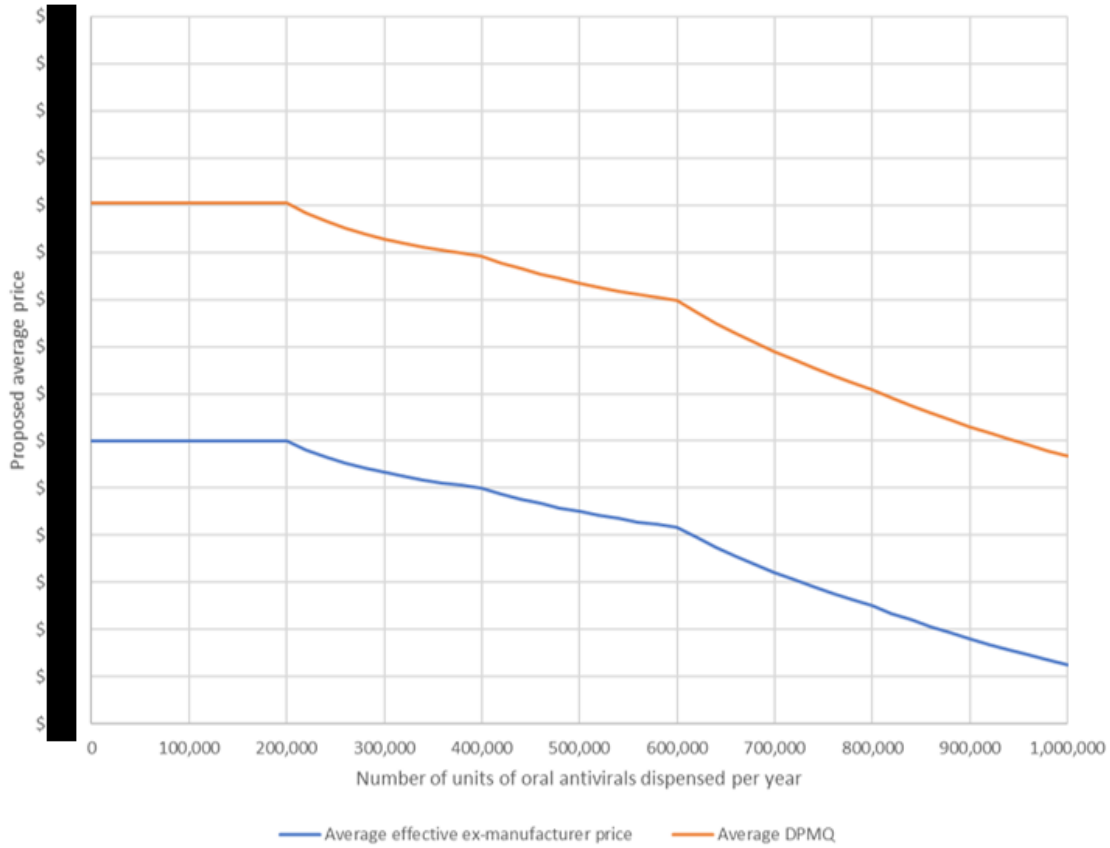
Source: Molnupiravir submission 22 September 2023 and corrected DPMQ calculation during evaluation.

12.9 The ESC noted that tiered pricing shown in Table 19 results in progressively reduced effective ex-manufacturer price and effective DPMQ for molnupiravir by volume of

[21] https://clinicalevidence.net.au/covid-19/, accessed 3 October 2023.

OAVs dispensed as shown in Figure 5 and Table 20. Although the pricing for a tier drops significantly by tiers, the average DPMQ reduces slowly with increasing utilisation of the oral antivirals (e.g., the DPMQ for additional units of molnupiravir supplied after 800,000 units of oral antivirals have been dispensed is $ [redacted], but the average DPMQ of molnupiravir when 820,000 units of oral antivirals have been dispensed is $ [redacted].

**Figure 5: Molnupiravir average effective ex-manufacturer price and DPMQ by volume of oral antivirals for COVID-19**




Source: Prepared during evaluation.

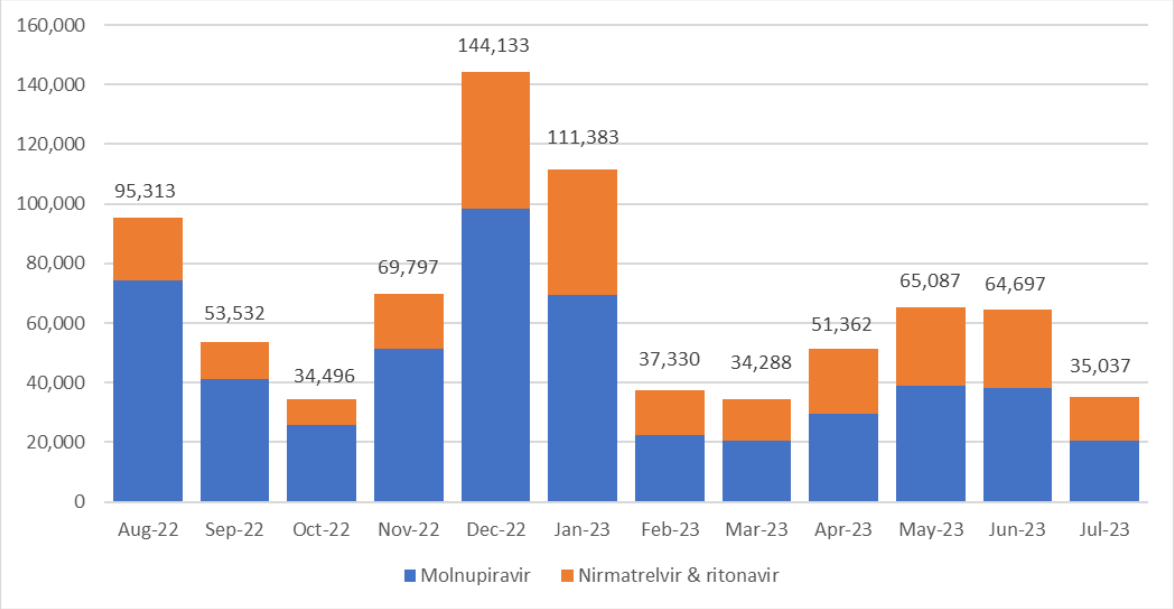
**Table 20: Effective average ex-manufacturer price and effective average DPMQ by utilisation of OAVs for COVID-19**

| Total utilisation of oral antivirals for COVID-19 | Average effective ex-manufacturer price of molnupiravir | | Average effective DPMQ | |
|---|---|---|---|---|
| 1 | | | | |
| 200,000 | | | | |
| 300,000 | | | | |
| 400,000 | | | | |
| 500,000 | | | | |
| 600,000 | | | | |
| 700,000 | | | | |
| 800,000 | | | | |
| 900,000 | | | | |
| 1,000,000 | | | | |

Source: Prepared during evaluation

12.10 The submission stated that the AEMP of $ [redacted] is a three year average price for the duration of the RSA on a base case OAV volume of approximately 400,000 OAV units per year, calculated as per the proposed MOV price OAV volume tiers (see 'AEMP calculation', MOV RSA Structure Workbook). The ESC noted that approximately 796,000 prescriptions for an oral antiviral were dispensed in the year ending 31July 2023 as shown in Figure 6. The lowest rate of prescribing was seen in March 2023 (approximately 34,000 units); at this baseline level of use, 408,000 prescriptions for oral antivirals per year can be anticipated.

**Figure 6: Total prescriptions dispensed for nirmatrelvir and ritonavir and for molnupiravir by month**




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

12.11 The ESC considered that future usage of OAVs was uncertain, and therefore did not support pricing tiers based on this approach. The ESC noted that the sponsor's anticipated average price may not be realised in practice (average ex-manufacturer price of $ [redacted] over 3 years).

*For more detail on PBAC's view, see section 14 PBAC outcome.*

# 13 Consideration of the evidence

## *Sponsor hearing*

13.1 There was no hearing for this item.

## *Consumer comments*

13.2 The PBAC noted that no consumer comments were received for this item. Previously the PBAC considered 18 comments from individuals and organisations in relation to molnupiravir at the July 2023 meeting (see paragraphs 6.7 to 6.10).

## *Clinical evidence*

13.3 No changes were made to the evidence base presented in the previous submission (see Table 5). However, the submission applied the relative risk reduction from the ≥ 65 year subgroup in PANORAMIC for patients in the 70+ subgroup and the 50-69 year subgroup of the economic model (see Table 21). The ESC considered that the uncertainties previously noted in regard to the magnitude of any benefit for molnupiravir in terms of effectiveness compared to no use of antivirals continue to apply.

**Table 21: Changes to evidence used to inform cost-effectiveness analyses**

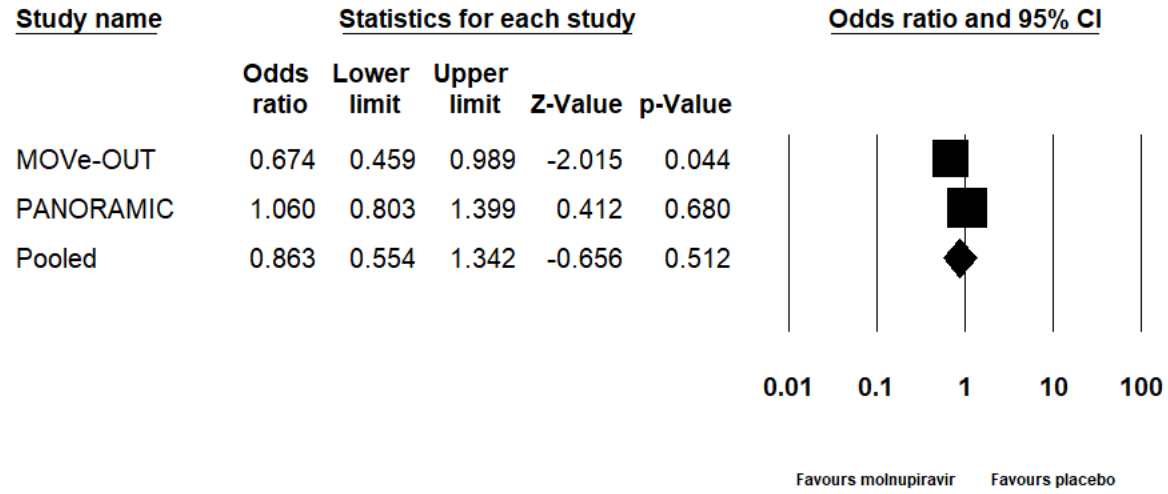
| Population | Data source in previous submission | Data source in submission | Key differences |
|---|---|---|---|
| ≥ 70 years | VIC data set | PANORAMIC | Decrease in reduction of death associated with molnupiravir: From a 54% reduction to 24%* reduction |
| ≥ 18 years & immunocompromised or previously hospitalised for COVID-19 | Evans et al. 2023 | Evans et al. 2023 | No difference |
| 50-69 year olds with ≥ 2 risk factors | Assumed the same as ≥ 70 years subgroup | | |
| Aboriginal and Torres Strait Islander people | Not explicitly modelled | | |

* VIC data set was based on risk reductions while PANORAMIC was based on odds ratios, so the risk reduction applied in the early re-entry model is actually ~23%

13.4 The PBAC previously advised that the overall body of evidence sourced from both randomised and observational trials, suggested that nirmatrelvir and ritonavir was likely more effective than molnupiravir (see paragraph 6.51). Although the submission claims advantages for molnupiravir in terms of safety versus nirmatrelvir and ritonavir, the limitations of the available data mean that the evidence cannot be considered sufficient to support such a claim.

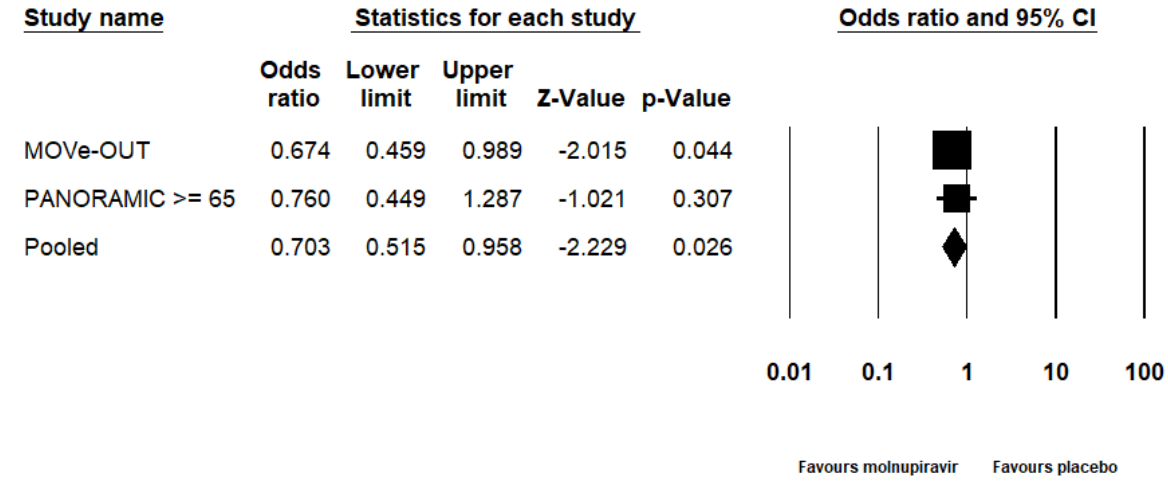
13.5 A meta-analysis of results (odds ratios) for the composite endpoint of hospitalisation or death from the molnupiravir trials (MOVe-OUT and PANORAMIC) is presented in Figure 7 (ITT populations). A second meta-analysis of results (odds ratios) is presented for MOVe-OUT and the ≥ 65 year subgroup from PANORAMIC in Figure 8 (reflecting high-risk patients in the RCTs).

**Figure 7: Meta-analysis of results (odds ratios) for the composite endpoint of hospitalisation or death from the molnupiravir trials (MOVe-OUT and PANORAMIC)**




Data sources: Conducted during the evaluation. The results section of the published report (Jayk-Bernal 2021) provided raw numbers to permit derivation of the odds ratio in the MOVe-OUT trial (48/709 in the molnupiravir arm and 68/699 in the placebo arm), Table 2 of the published report (Butler 2023) of the PANORAMIC trial directly provided the adjusted odds ratio.

**Figure 8: Meta-analysis of results (odds ratios) for the composite endpoint of hospitalisation or death from the molnupiravir trials (MOVe-OUT and the ≥ 65 year subgroup from PANORAMIC)**




Data sources: Conducted during the evaluation. The results section of the published report (Jayk-Bernal 2021) provided raw numbers to permit derivation of the odds ratio in the MOVe-OUT trial (48/709 in the molnupiravir arm and 68/699 in the placebo arm), Figure 2 of the published report (Butler 2023) of the PANORAMIC trial directly provided the adjusted odds ratio for the ≥ 65 year subgroup.

13.6 The ESC recalled that Evans 2023[22] was a retrospective cohort study of the effect of molnupiravir, nirmatrelvir and ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales, in which only 29.5% of treated patients received molnupiravir. The ESC considered that evidence from Evans

[22] Evans A, et al. Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: A retrospective cohort study. J Infect. 2023 Apr;86(4):352-360. doi: 10.1016/j.jinf.2023.02.012. Epub 2023 Feb 10.

2023 was not robust enough to justify an assumption of more favourable treatment effect in the immunocompromised subgroup as proposed by the submission (see paragraph 13.13).

13.7 Two additional publications were discussed in the submission:

- Cho et al, 2023[23], a study assessing in vitro antiviral activity of remdesivir, molnupiravir, and nirmatrelvir against Omicron subvariants.
- Lin et al 2023[24], a cohort study of patients who received a diagnosis of COVID-19 at the Cleveland Clinic between April 2022 and February 2023.

13.8 The PBAC recalled that in July 2023, a pre-print manuscript for the Victorian dataset was available (see paragraph 7.6), and noted that the final study publication had become available prior to the November 2023 PBAC meeting (van Heer 2023[25]).

## *Economic analysis*

13.9 The fundamental model structure was unchanged from the previous submission.

13.10 The main change to the modelling was the application of the relative risk reduction from the ≥ 65 year subgroup in PANORAMIC for patients in the 70+ subgroup and the 50-69 year subgroup. This estimate of treatment effect is slightly less favourable than the treatment effect applied from the retrospective cohort study conducted in Victoria, as originally applied. However, the ESC noted that the impact of this change in the 70+ subgroup was mitigated by the application of an increased baseline risk of hospitalisation. Baseline risk of hospitalisation as observed in the Victorian data was applied.

13.11 The ESC considered that the baseline risks of hospitalisation and death applied in the model were potentially overestimated. The ESC noted that the risk of an admission to an ICU in hospitalised patients applied in the submission's model was higher for the 50-69 year olds than the 70+ year olds. It thus considered that the risk of ICU admission was overestimated in the 50-69 year olds. The pre-PBAC response noted that that the risk of ICU admission in the submission was based on data from NSW COVID epidemiological reports, however the PBAC agreed with the ESC that the sponsor's model lacked face validity with regard to the risk of ICU admissions.

13.12 In the case of the immune compromised group, the submission did not make any changes to inputs and both the baseline risk of hospitalisation or death and the treatment effect were taken from a retrospective observational study conducted in

[23] Cho et al, 2023, Evaluation of antiviral drugs against newly emerged SARS-CoV-2 Omicron subvariants, Antiviral Res. 2023 Jun; 214: 105609. Published online 2023 Apr 20.
[24] Lin DY, et al. Nirmatrelvir or Molnupiravir Use and Severe Outcomes From Omicron Infections. JAMA Netw Open. 2023 Sep 5;6(9):e2335077.
[25] 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

Wales (Evans 2023). Thus, estimates of cost-effectiveness in this subgroup of patients were considered by the ESC to be associated with substantial uncertainty.

13.13 The ESC noted the key inputs to the model as follows:

- Baseline risk of hospitalisation
  - ≥ 70 years – increased to 11.9% (based on van Heer 2023 i.e., Victorian analysis) from 6.41%
  - ≥ 18 years Immunocompromised or prior hospitalisation – unchanged at 10.9%
  - Aboriginal and Torres Strait Islander people – not modelled explicitly
  - 50-69 year olds with ≥ 2 risk factors – unchanged at 1.77%
- Risk of ICU admission if hospitalised
  - 7.5%[26] for those aged ≥ 70 years and those ≥ 18 years & immune compromised & Aboriginal or Torres Strait Islander people aged ≥ 30 years with ≥ 1 risk factor
  - 14.3%[27] for those aged 50-69 years with ≥ 2 risk factors for developing severe COVID 19 The application of a higher risk of ICU admission for the lower risk group appears to lack face validity.
- Baseline risk of death
  - ≥ 70 years – 3.4% based on van Heer 2023 (i.e., Victorian analysis). This could be considered a high rate.
  - ≥ 18 years Immunocompromised or prior hospitalisation – 3.11% This could be considered a high rate.
  - Aboriginal and Torres Strait Islander people – not modelled explicitly.
  - 50-69 year olds with ≥ 2 risk factors – 0.07% based on NSW data.
- Background discounted QALYs lost for fatal cases
  - ≥ 70 years – 4.0
  - ≥ 18 years Immunocompromised or prior hospitalisation – 11.6
  - Aboriginal and Torres Strait Islander people – not modelled explicitly.
  - 50-69 year olds with ≥ 2 risk factors – 11.2

- Treatment effect
  - OR applied:
    - 0.76 (based on PANORAMIC subgroup aged ≥ 65 years) applied for the ≥ 70 years subgroup and the 50-69 year olds with ≥ 2 risk factors;
    - 0.65 for those aged ≥ 18 years & immune compromised or prior hospitalisation for COVID 19 based on Evans 2023 (a retrospective cohort study conducted in Wales).

13.14 Corrected weighted ICERs for scenarios by extent of utilisation are summarised in Table 22. The effective price for molnupiravir based on the utilisation estimates in

[26] 70+ group: 0.89%/11.9% (refer MOV_CEM_Australia_22 September.xlsm (=Inputs!C15/Inputs!C14)

[27] 50-69, +2RF group: 0.13%/0.93% (refer MOV_CEM_Australia_22 September.xlsm (=Inputs!D15/Inputs!D14)

Year 1, was applied for each of the utilisation scenarios. The ICER for molnupiravir in patients aged 50-69 years with 2 or more risk factors for severe COVID 19 necessitating hospitalisation was substantially higher than those calculated for the 70+ or immune compromised subgroups. No estimate of the ICER in the high risk Aboriginal and Torres Strait Islander population was presented. The ESC noted that, although the weighted ICER was $5,000 to < $15,000/QALY gained with each of the modelled prices, the results varied widely for the subpopulations and it was uncertain whether the proposed inputs (paragraph 13.13) were appropriate for estimating the cost-effectiveness of molnupiravir.

**Table 22: Results of cost-effectiveness analyses by extent of utilisation (prepared during the evaluation)**

| Scenario (utilisation in 2024) | Assumed effective molnupiravir price (DPMQ) ($) | Incremental costs ($) | Incremental QALYs | Weighted ICER[a] ($) | ICER 70+ ($) | ICER 18+ IC ($) | ICER 50-69 2RF ($) |
|---|---|---|---|---|---|---|---|
| **Base case 397,351 units** | [redacted] | [redacted] | 0.0545 | [redacted][1] | [redacted][1] | [redacted][2] | [redacted][3] |
| **Low 227,344 units** | [redacted] | [redacted] | 0.0545 | [redacted][1] | [redacted][1] | [redacted][2] | [redacted][3] |
| **Med 595,862 units** | [redacted] | [redacted] | 0.0545 | [redacted][1] | [redacted][1] | [redacted][2] | [redacted][4] |
| **High 784,658 units** | [redacted] | [redacted] | 0.0545 | [redacted][1] | [redacted][1] | [redacted][2] | [redacted][4] |

a. Proportion of each population: 70+ = 60.7%; 50-69 with RF=19.1%; 18-69 and immunocompromised; 20.2%

*The redacted values correspond to the following ranges:*

[1] *$5,000 to < $15,000*

[2] *$0 to < $5,000*

[3] *$75,000 to < $95,000*

[4] *$55,000 to < $75,000*

13.15 With reference to Table 22, the pre-PBAC response stated that cost effectiveness was robust across the patient populations with a weighted ICER of $5,000 to < $15,000/QALY. However, the PBAC considered that some of the sponsor's proposed inputs were unreasonably favourable to the intervention (paragraph 13.13) and were therefore not appropriate for estimating the cost-effectiveness of molnupiravir.

13.16 The COVID-19 mortality estimates from CoRiCal (COVID-19 Risk Calculator) are shown in Figure 9. The pre-PBAC response stated that the mortality rate of 3.4% for the ≥70 year old group applied in the economic model was based on the Victorian analysis, which was a direct measurement of the risk of death in a highly applicable population with varying levels of disease severity and vaccination status. The response considered that the CoRICal estimates were less reliable than the mortality data from van Heer as the mortality risk was calculated, rather than based on direct evidence. The response also stated that the CoRICal breakdown of mortality risk by vaccination status is outdated, as it reflects the situation in early 2022, when the majority of elderly Australians had received a recent vaccination. It was 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 months[28].

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

IMMUNISATION COALITION

**RISK OF DYING FROM COVID-19**

**Estimated deaths per 10,000 COVID-19 cases by age, sex, and vaccination status**

**Australia, January 2022. Version 2.0.**

(based on circulating variants = 90% omicron and 10% delta)

AZ=AstraZenca COVID-19 vaccine. Pfz = Pfizer COVID-19 vaccine. Mod = Moderna COVID-19 vaccine.

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Flinders UNIVERSITY

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| Gender | Age group (years) | Not vaccinated | 1 dose of AZ (3 weeks ago) | 2 doses of AZ (2nd dose less than 2 mths ago) | 2 doses of AZ (2nd dose 2 to 4 mths ago) | 2 doses of AZ (2nd dose 4 to 6 mths ago) | 2 doses of AZ + Pfz or Mod booster (2 mths ago) | 1 dose of Pfz (3 weeks ago) | 2 doses of Pfz (2nd dose less than 2 mths ago) | 2 doses of Pfz (2nd dose 2 to 4 mths ago) | 2 doses of Pfz (2nd dose 4 to 6 mths ago) | 2 doses of Pfz + Pfz or Mod booster (2 mths ago) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Male | 12-19 | 0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 |
| | 20-29 | 0.3 | 0.1 | 0.1 | 0.1 | 0.2 | <0.1 | 0.1 | 0.1 | 0.1 | 0.1 | <0.1 |
| | 30-39 | 1.4 | 0.4 | 0.4 | 0.4 | 0.6 | 0.1 | 0.3 | 0.2 | 0.2 | 0.4 | 0.1 |
| | 40-49 | 4 | 1.0 | 0.7 | 0.8 | 1.3 | 0.2 | 0.8 | 0.4 | 0.4 | 0.8 | 0.2 |
| | 50-59 | 11 | 3 | 2 | 2 | 4 | 0.4 | 2 | 1.0 | 1.0 | 2 | 0.4 |
| | 60-69 | 38 | 9 | 6 | 7 | 12 | 1.4 | 7 | 3 | 3 | 7 | 1.4 |
| | 70+ | 362 | 98 | 74 | 80 | 134 | 18 | 75 | 42 | 42 | 83 | 18 |
| Female | 12-19 | 0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 |
| | 20-29 | 0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 |
| | 30-39 | 0.4 | <0.1 | <0.1 | <0.1 | 0.1 | <0.1 | 0.1 | <0.1 | <0.1 | <0.1 | <0.1 |
| | 40-49 | 1.6 | 0.4 | 0.3 | 0.3 | 0.6 | 0.1 | 0.3 | 0.2 | 0.2 | 0.3 | 0.1 |
| | 50-59 | 7 | 2 | 1.5 | 1.6 | 3 | 0.4 | 1.4 | 0.8 | 0.8 | 1.6 | 0.4 |
| | 60-69 | 22 | 7 | 6 | 6 | 10 | 1.4 | 5 | 3 | 3 | 6 | 1.4 |
| | 70+ | 322 | 77 | 55 | 61 | 106 | 13 | 62 | 31 | 31 | 63 | 13 |

Estimated deaths per 10,000 cases

- Less than 0.1
- 0.11 to 1.0
- 1.1 to 10
- 10.1 to 50
- 50.1 to 150
- More than 150

***IMPORTANT NOTES***

* Chart only shows risk of dying from COVID-19, but there are other potential long-term complications, such as Long COVID.
* Each dose of vaccine takes about 2 weeks to work.
* Calculations based on circulating variants = 90% omicron and 10% delta. Results might differ for other variants.
* Calculations based on population-level data and do not take into account individual comorbidities.
* Case fatality rates for Omicron based on reported cases & deaths in Australia during Omicron circulation, but true case numbers are unknown because of limited testing. Chart will be updated as more data become available.
* Deaths likely to be higher in people with serious medical problems and in vulnerable groups.
* Deaths likely to be higher if health systems are overwhelmed.
* There are only minor differences between the effectiveness of Pfizer and Moderna boosters against death. Both are highly effective.

Estimates based on CoRiCal (COVID-19 Risk Calculator): https://corical.immunisationcoalition.org.au.
Questions & feedback to Prof Colleen Lau, University of Queensland: colleen.lau@uq.edu.au

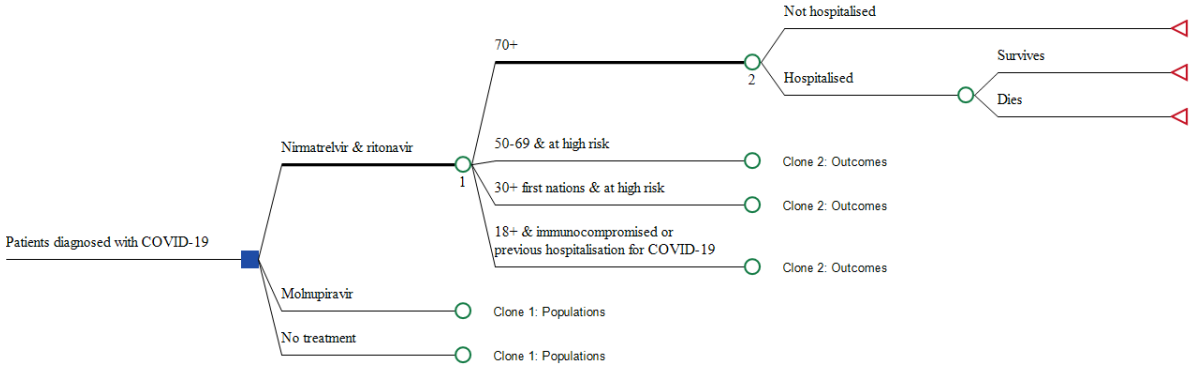
## *Revised economic analysis*

13.17 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.

13.18 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.

[28] 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.

**Figure 10: Structure of the common model**




13.19 The key inputs applied in the sponsor's model and the common model are summarised in Table 23. 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 23:Comparison of key inputs applied in the common model with those applied in the submission's model**

| Parameter | Common model | Molnupiravir submission |
|---|---|---|
| Baseline risk of hospitalisation | | |
| 70+ | 5% | 11.9% |
| 50-69 with ≥ 2 risk factors | 2% | 1.77% |
| First Nations | 3% | Not modelled |
| 18+ and immune compromised | 4% | 10.9% |
| Proportion of hospitalised patients requiring admission to ICU | | |
| 70+ | 10% | 7.5% |
| 50-69 with ≥ 2 risk factors | 5% | 14.3% |
| First Nations | 10% | Not modelled |
| 18+ and immune compromised | 10% | 7.5% |
| Baseline risk of death in the acute phase following COVID-19 | | |
| 70+ | 1%@ | 3.4% |
| 50-69 with ≥ 2 risk factors | 0.33%@ | 0.07% |
| First Nations | 0.67%@ | Not modelled |
| 18+ and immune compromised | 1%@ | 3.11% |
| Treatment effect (odds ratio) for molnupiravir | | |
| 70+ | 0.76 | 0.76^ |
| 50-69 with ≥ 2 risk factors | 0.76 | 0.76^ |
| First Nations | 0.76 | Not modelled |
| 18+ and immune compromised | 0.76 | 0.65^ |
| Discounted QALYs lost by a patient who dies due to COVID-19 | | |
| 70+ | 6.44 | 4.0315 |
| 50-69 with ≥ 2 risk factors | 12.18 | 11.2805 |
| First Nations | 13.00 | Not modelled |
| 18+ and immune compromised | 15.57 | 11.778 |
| Cost of hospitalisation | | |
| General ward | $6,419[&] | $13,684.43 |
| ICU | $20,675[#] | $29,508.63 |

Abbreviations: ICU = intensive care unit; N/A = not applicable

@ 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.

^ Source: high-risk subgroup of the PANORAMIC trial applied for the 70+ and 50-69 subgroups; Evans 2023 (a retrospective cohort study conducted in Wales) for the immune compromised subgroup. The same odds ratios were applied for both hospitalisation and death endpoints.

& weighted (by separation) average costs from the National Hospital Cost Data Collection (Public Sector, Round 23, 2018-2019) for AR-DRG items E62 A/B (Respiratory Infections and Inflammations)

# weighted (by separation) average costs from the National Hospital Cost Data Collection (Public Sector, Round 23, 2018-2019) for AR-DRG items E40/41 A/B (Respiratory System Disorders with Ventilator Support / Respiratory System Disorders with Non-Invasive Ventilation)

13.20 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 24: Results of the respecified economic evaluation conducted during the evaluation – molnupiravir**

| | Molnupiravir | Placebo | Increment | ICER per QALY |
|---|---|---|---|---|
| **Cohort: Aged ≥ 70** | | | | |
| Costs ($) | [redacted] | $392.23 | [redacted] | [redacted][1] |
| QALYS lost | -0.0495 | -0.0644 | 0.0149 | |
| **Cohort: Aged ≥18 and immune-compromised** | | | | |
| Costs ($) | [redacted] | $313.78 | [redacted] | [redacted][2] |
| QALYS lost | -0.1195 | -0.1557 | 0.0362 | |
| **Cohort: Aboriginal and Torres Strait Islander people aged ≥ 30 and ≥ 1 risk factor** | | | | |
| Costs ($) | [redacted] | $235.34 | [redacted] | [redacted][3] |
| QALYS lost | -0.0663 | -0.0867 | 0.0203 | |
| **Cohort: Aged 50-69 & ≥ 2 risk factors** | | | | |
| Costs ($) | [redacted] | $142.64 | [redacted] | [redacted][4] |
| QALYS lost | -0.0310 | -0.0406 | 0.0096 | |
| **Current Scenario[a] – Overall ICER with current restrictions and proportions based on utilisation[c]** | | | | |
| Costs ($) | [redacted] | $310.47 | [redacted] | [redacted][1] |
| QALYS lost | -0.0549 | -0.0715 | 0.0166 | |
| **Revised Scenario[b] – Overall ICER with price reduction corresponding to PBAC advice (ICER ≤$15,000/QALY in all subgroups)[c]** | | | | |
| Costs ($) | [redacted] | $310.47 | [redacted] | [redacted][5] |
| QALYS lost | -0.0549 | -0.0715 | 0.0166 | |

[a] The risk-share proposal proposed in the molnupiravir submission means that a fixed price does not apply for molnupiravir. The effective DPMQ for molnupiravir reduces as volume increases. The price applied for molnupiravir in the common model assumes utilisation of oral antivirals of 766,498 units, which is similar to utilisation over the past 12 months, which results in an effective ex-manufacturer price of $ [redacted] per pack (equating to an effective DPMQ of $ [redacted]).

[b] The molnupiravir weighted DPMQ in the revised scenario is $ [redacted] ([redacted]% reduction from proposed Tier 1 price DPMQ of $ [redacted] based on AEMP of $ [redacted] and [redacted]% reduction from the current DPMQ of $1,102.24). The effective DPMQ for each individual subgroup is shown in Table 25.

[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 25.

*The redacted values correspond to the following ranges:*

*[1] $35,000 to < $45,000*

*[2] $15,000 to < $25,000*

*[3] $25,000 to < $35,000*

*[4] $55,000 to < $75,000*

*[5] $5,000 to < $15,000*

13.21 The revised scenario in Table 24 corresponds to PBAC advice that the ICER should be no greater than $15,000/QALY in any subgroup (see paragraph 14.8). The effective DPMQ corresponding to this ICER threshold in each individual subgroup is shown in Table 25, as well as the assumed distribution of patients across populations used for calculation of the weighted effective DPMQ. The PBAC noted the results suggest that a substantial price reduction is required to achieve cost-effectiveness based on plausible inputs.

**Table 25: Effective DPMQ of molnupiravir 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] |

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

13.22 The PBAC noted the limitations of the evidence base available to inform the treatment effect assumed to be associated with molnupiravir in the economic model (Table 6),

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.

13.23 A multivariate sensitivity analysis (MSA) was conducted and the results are presented in Table 26 to explore these uncertainties. This analysis applies assumptions that are more favourable to the intervention than was applied in the evaluation common model shown in Table 23, 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 molnupiravir, OR = 0.703 (see Figure 8).
- Baseline risks of death are increased by 50% compared to those applied in the base common evaluation 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.

13.24 The PBAC's advice in relation to the MSA is provided in paragraph 14.12.

**Table 26: Results of the alternative economic evaluation – molnupiravir (multivariate sensitivity analysis)**

| | Molnupiravir | Placebo | Increment | ICER per QALY |
|---|---|---|---|---|
| **Cohort: Aged ≥ 70** | | | | |
| Costs | [redacted] | $1,026.64 | [redacted] | [redacted][1] |
| QALYS lost | -0.0284 | -0.0689 | 0.0277 | |
| **Cohort: Aged ≥18 and immune-compromised** | | | | |
| Costs | [redacted] | $969.99 | [redacted] | [redacted][2] |
| QALYS lost | -0.0680 | -0.1662 | 0.0674 | |
| **Cohort: Aboriginal and Torres Strait Islander people aged ≥ 30 and ≥ 1 risk factor** | | | | |
| Costs | [redacted] | $913.68 | [redacted] | [redacted][1] |
| QALYS lost | -0.0376 | -0.0922 | 0.0378 | |
| **Cohort: Aged 50-69 & ≥ 2 risk factors** | | | | |
| Costs | [redacted] | $847.62 | [redacted] | [redacted][3] |
| QALYS lost | -0.0175 | -0.0431 | 0.0178 | |
| **MSA Current Scenario[a] – Overall ICER with current restrictions and proportions based on utilisation[c]** | | | | |
| Costs | [redacted] | $967.90 | [redacted] | [redacted][1] |
| QALYS lost | -0.0313 | -0.0763 | 0.0309 | |
| **MSA Revised Scenario[b] – Overall ICER with price reduction corresponding to PBAC advice (ICER ≤$15,000/QALY in all subgroups)[c]** | | | | |
| Costs | [redacted] | $749.42 | [redacted] | [redacted][2] |
| QALYS lost | -0.0313 | -0.0763 | 0.0309 | |

a. The risk-share proposal proposed in the molnupiravir submission means that a fixed price does not apply for molnupiravir. The effective DPMQ for molnupiravir reduces as volume increases. The price applied for molnupiravir in the common model assumes utilisation of oral antivirals of 766,498 units, which is similar to utilisation over the past 12 months, which results in an effective ex-manufacturer price of $ [redacted] per pack (equating to an effective DPMQ of $ [redacted]).

b. The molnupiravir weighted DPMQ in the revised scenario is $ [redacted] ( [redacted]% reduction from proposed Tier 1 price DPMQ of $ [redacted] based on AEMP of $ [redacted]).

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 25.

*The redacted values correspond to the following ranges:*

[1] *$15,000 to < $25,000*

[2] *$5,000 to < $15,000*

[3] *$35,000 to < $45,000*

## *Drug cost/patient/course*

13.25 The proposed dispensed price per course of treatment with molnupiravir is $ [redacted] based on the Tier 1 price proposed in the submission.

## *Estimated PBS usage & financial implications*

13.26 This submission was not considered by DUSC.

13.27 Financial estimates in a range of scenarios (base case, low use, medium use, and high use) were presented in the submission. Estimates (corrected) of annual expenditure on molnupiravir range from $100 million to < $200 million in Year 1 of the low use scenario to $300 million to < $400 million in Year 6 in the high use scenario (Table 27).

13.28 The submission claimed that, based on feedback from GPs regarding the broad range of situations where nirmatrelvir and ritonavir is unsuitable, a 55% market share for molnupiravir should be maintained. The ESC considered this was an overestimate of the extent of use that would be appropriate for molnupiravir, given that dose reductions or pausing of treatments that potentially interact with nirmatrelvir and

ritonavir is possible in a substantial proportion of patients in whom a potential interaction is reported. The PBAC noted that some sources estimated a much lower proportion of patients would be unsuitable for treatment with nirmatrelvir and ritonavir, such as two publications that reported approximately 15% of patients had a possible contraindication (Lim 2022[29] and Hoertel 2022[30]). The PBAC noted that the utilisation of molnupiravir in Australia appeared relatively high compared with other countries, for example in September 2023 it was reported that molnupiravir had comprised approximately 3% of all oral antiviral dispensing in New Zealand in recent months[31].

13.29 The submission modelled scenarios reflecting COVID waves of varying amplitudes based on variations observed in annual flu waves. The submission described these as follows:

- Base Case: to reflect an annual mild OAV wave, analogous to that observed in 2023 (19 week wave) with the remaining weeks estimated at background rate (4,372 OAV scripts, lowest week to date).
- Low scenario: based on 52 weeks of usage at the background rate (lowest OAV week so far).
- Medium scenario: analogous to two mild waves.
- High scenario: OAV scripts as observed in the 12 months ending August 2023 accounting for a large spike in utilisation as per Dec 22-Jan 23.

13.30 The submission stated that the Prescriber bag listing (Medical Practitioner and Nurse Practitioner) for molnupiravir (PBS item 13144T) may no longer be necessary, due to relatively low utilisation, and did not estimate utilisation for this item. The July 2023 submission estimated approximately 10,000 to < 20,000 Prescriber Bag prescriptions per year over six years, compared with 600,000 to < 700,000 prescriptions each year for the General Schedule listing of molnupiravir (Table 17). If the Prescriber bag listing is maintained, the utilisation for this item (shown in Table 17) must be added to the estimates.

13.31 Financial estimates presented in the submission (corrected to apply the appropriate dispensed prices) are summarised in Table 27. Note, this table assumes the proposed price tiers apply for 6 years (however the submission proposed a three year deed).

29 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.
30 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.
31 Decision to change the access criteria for COVID-19 antiviral treatments dated 20 September 2023, https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/2023-09-20-decision-on-covid-19-antivirals-access-criteria.

**Table 27:Financial estimates proposed in the submission[a]**

| **Base case** | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
|---|---|---|---|---|---|---|
| Total OAV market | 1 | 10 | 10 | 10 | 10 | 10 |
| Molnupiravir Rx | 2 | 2 | 2 | 2 | 2 | 2 |
| Effective average DPMQ ($) | | | | | | |
| **Total effective PBS expenditure for molnupiravir** | 3 | 3 | 3 | 3 | 3 | 8 |
| Patient co-payments | 4 | 4 | 4 | 4 | 4 | 4 |
| **Net government expenditure** | 3 | 3 | 3 | 3 | 3 | 3 |
| **Low case** | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
| Total OAV market | 2 | 2 | 2 | 2 | 2 | 2 |
| Molnupiravir Rx | 5 | 5 | 5 | 5 | 5 | 5 |
| Effective average DPMQ ($) | | | | | | |
| **Total effective PBS expenditure for molnupiravir** | 3 | 3 | 3 | 3 | 3 | 3 |
| Patient co-payments | 4 | 4 | 4 | 4 | 4 | 4 |
| **Net government expenditure** | 6 | 3 | 3 | 3 | 3 | 3 |
| **Medium case** | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
| Total OAV market | 7 | 12 | 12 | 12 | 12 | 12 |
| Molnupiravir Rx | 1 | 1 | 1 | 1 | 1 | 1 |
| Effective average DPMQ ($) | | | | | | |
| **Total effective PBS expenditure for molnupiravir** | 8 | 8 | 8 | 8 | 8 | 8 |
| Patient co-payments | 4 | 4 | 4 | 4 | 4 | 4 |
| **Net government expenditure** | 8 | 8 | 8 | 8 | 8 | 8 |
| **High case** | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
| Total OAV market | 9 | 13 | 13 | 13 | 13 | 15 |
| Molnupiravir Rx | 10 | 10 | 10 | 10 | 10 | 7 |
| Effective average DPMQ ($) | | | | | | |
| **Total effective PBS expenditure for molnupiravir** | 11 | 11 | 11 | 11 | 11 | 11 |
| Patient co-payments | 4 | 4 | 14 | 14 | 14 | 14 |
| **Net government expenditure** | 11 | 11 | 11 | 11 | 11 | 11 |

a. Estimated corrected to apply the appropriate dispensed prices. An average co-payment of $12.16 was assumed.

*The redacted values correspond to the following ranges:*

*[1] 300,000 to < 400,000*

*[2] 200,000 to < 300,000*

*[3] $100 million to < $200 million*

*[4] $0 to < $10 million*

*[5] 100,000 to < 200,000*

*[6] $90 million to < $100 million*

[7] *500,000 to < 600,000*
[8] *$200 million to < $300 million*
[9] *700,000 to < 800,000*
[10] *400,000 to < 500,000*
[11] *$300 million to < $400 million*
[12] *600,000 to < 700,000*
[13] *800,000 to < 900,000*
[14] *$10 million to < $20 million*
[15] *900,000 to < 1,000,000*

### *Financial Management – Risk Sharing Arrangements*

13.32 The submission proposed a 3-year price-volume agreement with pricing dependent on volume of oral antivirals (not based on molnupiravir use), including 5 tiers with 200,000 increments in prescription numbers.

*For more detail on PBAC's view, see section 14 PBAC outcome.*

## 14 PBAC Outcome

14.1 The PBAC provided advice regarding molnupiravir (Lagevrio), for the treatment of patients with mild to moderate Coronavirus disease (COVID-19) who are at high risk of severe disease requiring hospitalisation. Consistent with its July 2023 advice, the PBAC considered that molnupiravir may be an appropriate treatment for patients who cannot use nirmatrelvir and ritonavir (Paxlovid). The PBAC noted that nirmatrelvir and ritonavir is a more effective treatment than molnupiravir, however nirmatrelvir and ritonavir is contraindicated 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. The PBAC advised that the submission did not support continuation of the PBS listing with the current restriction criteria and proposed price of molnupiravir. The PBAC recommended changes to the restriction, and price of molnupiravir. The PBAC noted that the market share for molnupiravir remained higher than nirmatrelvir and ritonavir, which did not reflect clinical guidelines. 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.

14.2 The PBAC noted the submission's proposal to formalise the current administrative advice regarding suitability for nirmatrelvir and ritonavir as a new clinical criterion stating the drug should be considered for use only if nirmatrelvir and ritonavir is 'contraindicated or otherwise unsuitable'. To increase use of the most effective treatment option when clinically appropriate, the PBAC considered the restriction should limit eligibility to patients strictly contraindicated for nirmatrelvir and ritonavir. The PBAC considered that this change would be required to support continued listing.

14.3 The PBAC advised that an Authority Required (STREAMLINED) restriction level remained appropriate.

14.4 The PBAC advised that the Prescriber Bag listing should be maintained for molnupiravir to provide for patients requiring urgent treatment and contraindicated to nirmatrelvir and ritonavir. And the PBAC expected utilisation of the item to remain low (see paragraph 13.30).

14.5 The PBAC noted that the TGA approved Product Information for nirmatrelvir and ritonavir describes contraindications for use, including severe renal impairment, severe hepatic impairment and numerous drug-drug interactions. Nirmatrelvir and ritonavir is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. The PBAC proposed that a prescribing instruction should be added to the restriction for molnupiravir to refer prescribers to the Liverpool COVID-19 Drug interaction checker (www.covid19-druginteractions.org/checker) to assist with determination of contraindications to nirmatrelvir and ritonavir. The recommended restriction in Section 13 states that details of contraindications to nirmatrelvir and ritonavir can be found using the Liverpool COVID-19 Drug interaction checker or the TGA-approved Product Information for Paxlovid, and. The PBAC advised that when potential DDIs with nirmatrelvir and ritonavir are identified, the prescriber should consider if interacting regular medicines can be managed safely with additional monitoring and/or by temporarily withholding or adjusting the patient's other medications consistent with NCET advice[32]. The PBAC advised this remained a matter for prescriber judgement, and that the PBS restriction should specify that the reasons for contraindication to nirmatrelvir and ritonavir must be documented in the patient's medical records.

14.6 In the context of the proposed changes to the restriction, the PBAC considered that the market share for molnupiravir should fall substantially, noting that published studies reported that approximately 15% of the population had a possible contraindication to nirmatrelvir and ritonavir (paragraph 13.28). The PBAC's intention was that molnupiravir use should be restricted to a limited population with complex health needs (comorbidities) that require a treatment other than nirmatrelvir and ritonavir.

14.7 The PBAC noted that the submission proposed pricing tiers with ex-manufacturer prices between $ | to $ | for 40 capsules (Table 19), which corresponded to an average effective ex-manufacturer price of $ | based on the submission's utilisation estimates over 3 years. This compared with a proposed ex-manufacturer price of $ | for 40 capsules that was considered in July 2023. The current approved ex-manufacturer price (AEMP) is $988 for a pack of 40 capsules. The PBAC did not support the sponsor's pricing proposal based on a price-volume agreement and noted that the cost-effectiveness at the requested price was highly uncertain. The PBAC advised that a further price reduction is required from the price proposed in the submission because

[32] https://covid19evidence.net.au/wp-content/uploads/PAXLOVID-PRESCRIBING-GUIDE.pdf

cost-effectiveness had not been demonstrated.

14.8 The PBAC noted the large patient population that was forecast by the submission, of 400,000 to < 500,000 patients to be treated with OAV per year in the base case, and 900,000 to < 1,000,000 in one year of the submission's high case estimates (Table 27). The PBAC noted the significant budget impact that was estimated by the submission, 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.

14.9 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 24. Given the limitations of the data available (see paragraph 13.22), the PBAC advised that it was not appropriate to value molnupiravir based on the overall weighted ICER, and instead the cost-effectiveness of molnupiravir 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 25.

14.10 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 paragraph 1.2).

14.11 Consistent with its advice in July 2023, based on the currently available clinical evidence, the PBAC considered that a substantial reduction in price would be required to support continued listing. The rationale for the requested price reduction was to overcome the uncertainty in cost-effectiveness arising from, in the main, uncertain extent of clinical benefit in the target populations. The PBAC noted the uncertainties in the submission's economic evaluation described by the ESC (paragraphs 13.11 to 13.14). The PBAC considered that the submission did not demonstrate cost-effectiveness due to concerns about the inputs applied in the submission's model. However, the revised economic analysis based on a simplified model, showed that molnupiravir could be considered cost-effective if the price were to be reduced such that the ICER does not exceed $15,000/QALY in any of the patient subgroups (Table 24). 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 25.

14.12 Noting the limitations of the data available, the PBAC also considered the multivariate sensitivity analysis presented in Table 26. The PBAC advised that the more favourable assumptions examined in the MSA were not accepted and did not provide reliable

estimates for decision making.

14.13 The PBAC advised that on the basis of the revised economic evaluation, a substantial 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 molnupiravir (Table 24).

14.14 The PBAC noted that the estimated utilisation and therefore financials were uncertain and dependent on future patterns of antiviral usage and relative usage of molnupiravir compared with the alternative treatment (nirmatrelvir and ritonavir). 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. The PBAC considered it was appropriate to model utilisation scenarios as set out in the submission (Table 27). However, the PBAC also considered that a maximum market share of no more than % for molnupiravir was more appropriate after implementation of the proposed restriction changes, compared with % assumed by the submission, although it would take time to see this effect and over time this should reflect only patients strictly contraindicated for nirmatrelvir and ritonavir (approximately 15%, paragraph 13.28).

14.15 In view of the uncertain financial estimates, the PBAC considered that the listing of molnupiravir should be considered again in 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 molnupiravir alongside the abovementioned DUSC review to support the PBAC consideration in July 2026.

14.16 The PBAC noted that the current market share of molnupiravir does not reflect the context that a more effective drug is available. 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 may prepare a statement or letter to relevant colleges about the relatively high use of molnupiravir and advice in relation to quality of use medicines including appropriate choice of medicine when a medicine is required. 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.

14.17 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; see paragraph 6.83). 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.

14.18 The PBAC noted that this submission is not eligible for an Independent Review as it was not seeking an additional indication for molnupiravir on the PBS.

**Outcome:**
Advice Provided

# 15 Recommended listing

15.1 Amend existing listing as follows:
Additions are in italics and deletions are in strikethrough.

| **MEDICINAL PRODUCT**<br>**medicinal product pack** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|
| MOLNUPIRAVIR | | | | |
| Authority Required (STREAMLINED) | | | | |
| Molnupiravir 200 mg capsule, 40 | 1 | 40 | 0 | Lagevrio |
| Prescriber bag | | | | |
| Molnupiravir 200 mg capsule, 40 | 2 | 80 | 0 | Lagevrio |

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| **Category / Program:** General Schedule |
| **Prescriber type:** ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐ |
| **Restriction type:**<br>☒Authority Required (STREAMLINED) |
| **Administrative Advice:**<br>Note: No increase in the maximum quantity or number of units may be authorised.<br>Note: No increase in the maximum number of repeats may be authorised.<br>~~Note: This drug should be considered for use only if nirmatrelvir (&) ritonavir is contraindicated or otherwise unsuitable.~~<br>*Note: Special Pricing Arrangements apply* |
| **13759** |
| **Indication:** SARS-CoV-2 infection |
| **Clinical criteria:** |
| ~~This drug should be considered for use only if nirmatrelvir (&) ritonavir is contraindicated or otherwise unsuitable~~ ~~**AND**~~<br>*The treatment must be for use when nirmatrelvir (&) ritonavir is* ~~either (i)~~ contraindicated~~, (ii) otherwise unsuitable~~ **AND** |
| Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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<br>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. |
| Access to this drug through this restriction is permitted irrespective of vaccination status.<br>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.<br>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.<br>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection. |

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| ***Prescribing instructions:*** |
| *For the purpose of administering this restriction, the contraindications to nirmatrelvir (&) ritonavir can be found using the Liverpool COVID-19 Drug interaction checker or the TGA-approved Product Information for Paxlovid.*<br>*Details/reasons of contraindications to nirmatrelvir (&) ritonavir must be documented in the patient's medical records.* |
| ***Administrative advice:*** |
| *Details of the Liverpool COVID-19 Drug interaction checker can be found at: https://www.covid19-druginteractions.org/checker* |
| **Indication:** SARS-CoV-2 infection |
| **Clinical criteria:** |
| ~~This drug should be considered for use only if nirmatrelvir (&) ritonavir is contraindicated or otherwise unsuitable~~ **~~AND~~**<br>*The treatment must be for use when nirmatrelvir (&) ritonavir is* ~~either (i)~~ contraindicated~~, (ii) otherwise unsuitable~~ **AND** |
| Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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. |
| **Population criteria:** |
| Patient must be at least 18 years of age. |
| For the purpose of administering this restriction, 'moderately to severely immunocompromised' patients are those with:<br>1. Any primary or acquired immunodeficiency including:<br>a. Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders,<br>b. Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),<br>c. Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency; OR<br>2. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received:<br>e. Chemotherapy or whole body radiotherapy,<br>f. 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,<br>g. 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),<br>h. 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<br>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<br>4. Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies; OR<br>5. People with disability with multiple comorbidities and/or frailty.<br><br>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. |

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| Access to this drug through this restriction is permitted irrespective of vaccination status.<br>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.<br>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.<br>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection. |
| ***Prescribing instructions:*** |
| *For the purpose of administering this restriction, the contraindications to nirmatrelvir (&) ritonavir can be found using the Liverpool COVID-19 Drug interaction checker or the TGA-approved Product Information for Paxlovid.*<br>*Details/reasons of contraindications to nirmatrelvir (&) ritonavir must be documented in the patient's medical records.* |
| ***Administrative advice:*** |
| *Details of the Liverpool COVID-19 Drug interaction checker can be found at: https://www.covid19-druginteractions.org/checker* |
| **13748** |
| **Indication:** SARS-CoV-2 infection |
| **Clinical criteria:** |
| ~~This drug should be considered for use only if nirmatrelvir (&) ritonavir is contraindicated or otherwise unsuitable~~ **~~AND~~**<br>*The treatment must be for use when nirmatrelvir (&) ritonavir is* ~~either (i)~~ contraindicated~~, (ii) otherwise unsuitable~~ **AND** |
| Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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. |
| For the purpose of administering this restriction, high risk is defined as the presence of at least one of the following conditions:<br>1. The patient is in residential aged care<br>2. The patient has disability with multiple comorbidities and/or frailty<br>3. Neurological conditions, including stroke and dementia and demyelinating conditions<br>4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease<br>5. Heart failure, coronary artery disease, cardiomyopathies<br>6. Obesity (BMI greater than 30 kg/$m^2$)<br>7. Diabetes type I or II, requiring medication for glycaemic control<br>8. Renal impairment (eGFR less than 60mL/min)<br>9. Cirrhosis<br>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<br>11. Past COVID-19 infection episode resulting in hospitalisation.<br><br>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.<br>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.<br>Access to this drug through this restriction is permitted irrespective of vaccination status.<br>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record. |

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| 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.<br>This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.<br>**Note**<br>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 |
| ***Prescribing instructions:*** |
| *For the purpose of administering this restriction, the contraindications to nirmatrelvir (&) ritonavir can be found using the Liverpool COVID-19 Drug interaction checker or the TGA-approved Product Information for Paxlovid.*<br>*Details/reasons of contraindications to nirmatrelvir (&) ritonavir must be documented in the patient's medical records.* |
| ***Administrative advice:*** |
| *Details of the Liverpool COVID-19 Drug interaction checker can be found at: https://www.covid19-druginteractions.org/checker* |
| **Clinical criteria:** |
| ~~This drug should be considered for use only if nirmatrelvir (&) ritonavir is contraindicated or otherwise unsuitable~~ **~~AND~~**<br>The treatment must be for use when nirmatrelvir (&) ritonavir is ~~either (i)~~ contraindicated~~, (ii) otherwise unsuitable~~ **~~AND~~**<br>Patient must have received a positive polymerase chain reaction (PCR) test result; OR<br>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 both: (i) at least 50 years of age, (ii) at high risk. |
| 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:<br>1. The patient is in residential aged care,<br>2. The patient has disability with multiple comorbidities and/or frailty,<br>3. Neurological conditions, including stroke and dementia and demyelinating conditions,<br>4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease,<br>5. Heart failure, coronary artery disease, cardiomyopathies,<br>6. Obesity (BMI greater than 30 kg/$m^2$),<br>7. Diabetes type I or II, requiring medication for glycaemic control,<br>8. Renal impairment (eGFR less than 60mL/min),<br>9. Cirrhosis, or<br>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.<br><br>Details of the patient's medical condition necessitating use of this drug must be recorded in the patient's medical records.<br>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.<br>Access to this drug through this restriction is permitted irrespective of vaccination status.<br>Where PCR is used to confirm diagnosis, the result, testing date, location and test provider must be recorded on the patient record.<br>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. |

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| This drug is not PBS-subsidised for pre-exposure or post-exposure prophylaxis for the prevention of SARS-CoV-2 infection.<br>**Note**<br>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 |
| ***Prescribing instructions:*** |
| *For the purpose of administering this restriction, the contraindications to nirmatrelvir (&) ritonavir can be found using the Liverpool COVID-19 Drug interaction checker or the TGA-approved Product Information for Paxlovid.*<br>*Details/reasons of contraindications to nirmatrelvir (&) ritonavir must be documented in the patient's medical records.* |
| ***Administrative advice:*** |
| *Details of the Liverpool COVID-19 Drug interaction checker can be found at: https://www.covid19-druginteractions.org/checker* |

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

# 16 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.

# 17 Sponsor's Comment

MSD will endeavour to work with the PBAC to ensure molnupiravir continues to be available for vulnerable COVID - positive patients who are contraindicated to other antivirals.