Molnupiravir for SARS-COV-2-infection: utilisation analysis

Drug utilisation sub-committee (DUSC)

October 2024

Abstract

Purpose

To review molnupiravir for the treatment of severe acute respiratory syndrome coronavirus 2 (COVID-19) as requested by DUSC at its June 2024 meeting.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Molnupiravir was PBS listed on 1 March 2022.

Data Source / methodology

Data extracted from the PBS database maintained by Department of Health and Aged Care, processed by Services Australia were used for the analyses.

Key Findings

- In the first year of PBS listing, 492,941 patients were supplied 509,307 molnupiravir prescriptions. In the second year of PBS listing, 348,052 patients were supplied 361,341 molnupiravir prescriptions.
- Most patients treated with molnupiravir were aged 70 years and older, with the most common age group being those aged between 70-74 years.
- Females accounted for a greater proportion of utilisation compared to males.
- General practitioners accounted for the majority of molnupiravir prescribing.
- Utilisation of molnupiravir in residential aged care facilities account for a small proportion of overall PBS utilisation.
- Molnupiravir accounted for a greater proportion of the COVID-19 oral antivirals market. However, its market share had decreased over time.

Purpose of analysis

To review molnupiravir for the treatment of severe acute respiratory syndrome coronavirus 2 (COVID-19) as requested by DUSC at its June 2024 meeting.

Background

Clinical situation

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. COVID-19 is spread by respiratory droplets or small airborne particles when an infected person coughs, sneezes, or talks, and is in close contact with others. Most people who are infected with COVID-19 experience mild to moderate symptoms such as fever, cough, tiredness and loss of smell.[1] However, some people are at high risk of becoming very ill from COVID-19 and requiring hospitalisation.[2] 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.

Pharmacology

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 ribonucleic acid (RNA) by the viral RNA polymerase results in an accumulation of errors in the viral genome leading to inhibition of replication.[3]

Therapeutic Goods Administration (TGA) approved indications

At the time of this review, molnupiravir had provisional approval 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.[3]

The decision to approve this indication was made on the basis of the analysis of efficacy and safety data from a Phase 3 trial. Continued approval of this indication depends on additional data.

[1] Australian Government Department of Health and Aged Care. About coronavirus disease 2019 (COVID-19). Accessed from https://www.health.gov.au/topics/covid-19/about

[2] Australian Government Department of Health and Aged Care. Groups at high risk from COVID-19. Accessed from: https://www.health.gov.au/topics/covid-19/protect-yourself-and-others/high-risk-groups

[3] Lagevrio®(molnupiravir). Australian Approved Product Information. Macquarie Park: Merck Sharp & Dohme (Australia) Pty Limited. Approved 20 January 2022 , updated 18 October 2023. Available from < https://www.tga.gov.au/product-information-pi.>

Molnupiravir is in the Black Triangle Scheme and is subject to additional monitoring in Australia to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events to the TGA.[4]

Dosage and administration

The recommended dose of molnupiravir in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.

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, including hospitalisation or death.[3]

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details

As at August 2024, molnupiravir was listed in:

- the General Schedule as an Authority Required (Streamlined) item (12910L)
- the Prescriber Bag (13144T).

Table 1: PBS listing of molnupiravir as at August 2024

Item code	Name, form & strength, pack size	Max qty packs	Rpts	DPMQ	Brand name and manufacturer
12910L	molnupiravir 200 mg capsule, 40	1	0	$1,102.71	Lagevrio® Merck Sharp & Dohme (Australia) Pty Ltd
13144T	molnupiravir 200 mg capsule, 40	2	0	$2,192.75	Lagevrio® Merck Sharp & Dohme (Australia) Pty Ltd

Source: the PBS website.
Notes:

- Details of the Liverpool COVID-19 Drug interaction checker can be found at: https://www.covid19-druginteractions.org/checker
- No increase in the maximum quantity or number of units may be authorised.
- No increase in the maximum number of repeats may be authorised.
- Special Pricing Arrangements apply.

[4] Therapeutic Goods Administration. The Black Triangle Scheme. Accessed 19 July 2024 from: https://www.tga.gov.au/resources/resource/guidance/black-triangle-scheme-information-sponsors

Restriction (abridged) as at August 2024

Molnupiravir was restricted for use in patients:

- Aged 70 years and older
- Aged 18 years and older, moderately to severely immunocompromised and at risk of progression to severe disease OR experienced past COVID-19 infection resulting in hospitalisation
- Aboriginal or Torres Strait Islander, aged 30 years and older with one risk factor.
- Aged between 50-69 years old with two risk factors.

Clinical criteria:

- The treatment must be for use when nirmatrelvir (&) ritonavir is contraindicated,

AND

- Patient must have received a positive polymerase chain reaction (PCR) test result; OR

- Patient must have received a positive rapid antigen test (RAT) result,

AND

- Patient must not require hospitalisation for COVID-19 infection at the time of prescribing,

AND

- The treatment must be initiated within 5 days of symptom onset; *OR*

- *The treatment must be initiated as soon as possible after a diagnosis is confirmed where asymptomatic (only for patients aged ≥70 years)*

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

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

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

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

For the purpose of administering this restriction, the contraindications to nirmatrelvir (&) ritonavir can be found using the Liverpool COVID-19 Drug interaction checker or the TGA-approved Product Information for Paxlovid.

Details/reasons of contraindications to nirmatrelvir (&) ritonavir must be documented 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.

Details regarding the risk factors and moderately to severely immunocompromised conditions can be found in Appendix A.

For details of the current PBS listing refer to the PBS website.

Changes to listing

Table 2 shows the changes in the eligible populations for molnupiravir since PBS listing.

Table 2: Overview of the changes in eligible populations for molnupiravir

<table>
<tr><th>March 2022</th><th>August 2022</th><th>November 2022</th><th>February 2023</th></tr>
<tr><td>65-74 years old,
2 risk factors</td><td colspan="3">50-69 years old,
2 risk factors</td></tr>
<tr><td>≥75 years old,
1 risk factor</td><td colspan="3">≥ 70 years old</td></tr>
<tr><td colspan="3">≥18 years old,
moderately to severely immunocompromised and at risk of progression to severe disease</td><td>≥18 years old,
(i) moderately to severely immunocompromised and at risk of progression to severe disease OR (ii) experienced past COVID-19 infection resulting in hospitalisation</td></tr>
<tr><td>ATSI,
≥50 years old,
2 risk factors</td><td>ATSI,
≥30 years old,
2 risk factors</td><td colspan="2">ATSI,
≥30 years old,
1 risk factor</td></tr>
</table>

Notes:

- ATSI= Aboriginal or Torres Strait Islander.
- The moderately to severely immunocompromised group extended the listing to include those who received abatacept in the last three months (August 2022) and those who received anti-CD20 monoclonal treatment in the last 12 months (January 2023).

Additional changes to the molnupiravir listing across all eligible population groups are noted in Table 3.

Table 3: Changes to overall molnupiravir listing

Date	Change to listing
May 2022	Addition of nurse practitioners as an additional prescriber type to verify RATs.
September 2022	Clarification that patient must not require hospitalisation for COVID-19 infection at the time of prescribing.
November 2022	Addition of the Prescriber Bag listing.
January 2023	Removal of requirement for the RAT to be verified by medical practitioner or nurse practitioner. Addition of administrative note stating molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable.
March 2024	Formalisation of clinical criterion in restriction stating the requirement for treatment only when contraindicated to nirmatrelvir (&) ritonavir.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

February 2022

The PBAC undertook an expedited consideration of a sponsor submission to add molnupiravir to the PBS for use in treating patients with mild to moderate COVID-19 who are at risk of developing severe disease requiring hospitalisation. The expedited consideration by PBAC recognises the urgent public health need related to the prevention, management, or treatment of SARS-CoV-2 infections.

The PBAC recommended the listing on the PBS of molnupiravir as a General Schedule, Authority Required (Streamlined) benefit.

The PBAC recommended PBS-subsidised treatment initially be provided for the following groups of patients with mild-moderate COVID-19 disease not requiring supplemental oxygen for their COVID-19 and where treatment is commenced within 5 days of the onset of symptoms:

- People 65 years or older with two additional high-risk factors for developing severe disease,
- People 75 years or older with one additional high-risk factor for developing severe disease,
- Moderately to severely immunocompromised people irrespective of vaccination status, and
- Aboriginal and Torres Strait Islander people aged 50 years or older with two additional high-risk factors for developing severe disease.

For further details refer to the Outcome Statement regarding the out-of-session PBAC recommendation in February 2022.

June 2022

The PBAC recommended changes to the PBS eligibility criteria for both molnupiravir and nirmatrelvir and ritonavir in the light of current understanding of the evidence for effectiveness and safety of these medicines, recent PBS utilisation patterns, and the changing epidemiology of COVID-19.

The PBAC recommended that treatment be provided as a General Schedule, Authority Required (Streamlined) benefit for the following groups of patients with COVID-19 disease not requiring supplemental oxygen for their COVID-19 and where treatment is commenced within 5 days of the onset of signs/symptoms for:

- People 50 years of age or older, with two additional risk factors for developing severe disease;
- People 30 years of age or older, identifying as Aboriginal or Torres Strait Islander, with two additional risk factors for developing severe disease;
- People 18 years of age or older, with moderate to severe immunocompromise; and
- People 70 years of age or older where treatment is commenced within 5 days of the onset of symptoms, or treatment is initiated as soon as possible after diagnosis is confirmed where asymptomatic.

The PBAC recommended changes to the list of conditions that define high risk for developing severe disease, including clarification and/or expansion of eligibility in relation to respiratory, cardiac, and neurological co-morbidity. The PBAC acknowledged that a large majority of Australian adults have received more than one COVID-19 vaccination, and recommended that the current condition 'patient has received less than 2 doses of SARS-CoV-2 vaccine' no longer need be included in the list.

The PBAC recommended changes to the definition of 'moderate to severe immunocompromise,' noting correspondence received from the Australian Rheumatology Association in relation to immunosuppression with use of methotrexate, azathioprine and abatacept.

For further details refer to the Outcome Statement regarding the out-of-session PBAC recommendation in June 2022.

July and November 2023 PBAC meetings

The PBAC provided advice regarding molnupiravir for the treatment of patients with mild to moderate 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. 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.

At its November 2023 meeting, the PBAC provided advice regarding molnupiravir, for the treatment of patients with mild to moderate 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. 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.

For further details refer to the Public Summary Document from the July and November 2023 PBAC meetings.

Methods

Data extracted from the PBS claims database maintained by the Department of Health and Aged Care and processed by Services Australia were used for the analyses. Prescription data were extracted from 1 March 2022 up to and including 30 June 2024.

Prescription data were used to determine the prescription and patient counts of molnupiravir by listing year and supply quarter. Analyses to examine utilisation following changes to the various changes to the sub-populations eligible for molnupiravir were also conducted. Sub-populations were determined by the corresponding Authority Required (Streamlined) code.

Data were also used to assess molnupiravir utilisation by the following analyses: age and gender distribution, prescriber type, residential aged care facility (RACF) (patients who are residents of an aged care facility are denoted by presence of a RACF Identification number [RACF Id]) and jurisdiction. As part of the jurisdiction analysis, patient numbers were standardised to provide a representative value relative to the population size of the respective state or territory. Population estimates for those aged between 18 years and over were extracted from the Australian Bureau of Statistics (ABS) for each state and territory. The number of patients were divided by the population estimates for each state and territory. These figures were multiplied by 100,000 to generate the age standardised values for each state and territory.

Additional prescription data were extracted for the other PBS-listed COVID-19 oral antiviral, nirmatrelvir and ritonavir, to assess market utilisation. A drug sequence analysis was conducted to examine the pattern of oral antiviral utilisation in patients. Two cohorts were selected for this analysis to compare therapy patterns before and after the formalisation of clinical criterion in the restriction requiring patients be treated with molnupiravir if they are contraindicated to nirmatrelvir and ritonavir. In both cohorts, the first prescribed drug was recorded and if patients were subsequently supplied other drugs, these were noted to form the patient's drug chronological sequence. As both molnupiravir and nirmatrelvir & ritonavir have listings on the Prescriber Bag, utilisation was examined based on their corresponding Prescriber Bag item codes.

As this analysis used date of supply prescription data, there may be small differences compared with publicly available Services Australia Medicare date of processing data.[5] The publicly available Services Australia Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included. The Services Australia Medicare data used in this report includes under co-payment prescriptions from 1 April 2012.

[5] PBS statistics. Australian Government Services Australia. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

Results

Analysis of drug utilisation

Overall utilisation

Table 4: Utilisation of molnupiravir by listing year

	Year 1	Year 2	Year 3 (part-year)
	March 2022 - February 2023	March 2023 - February 2024	March 2024 - June 2024
Patients treated	492,941	348,052	119,015
Prescriptions supplied	509,307	361,341	120,924

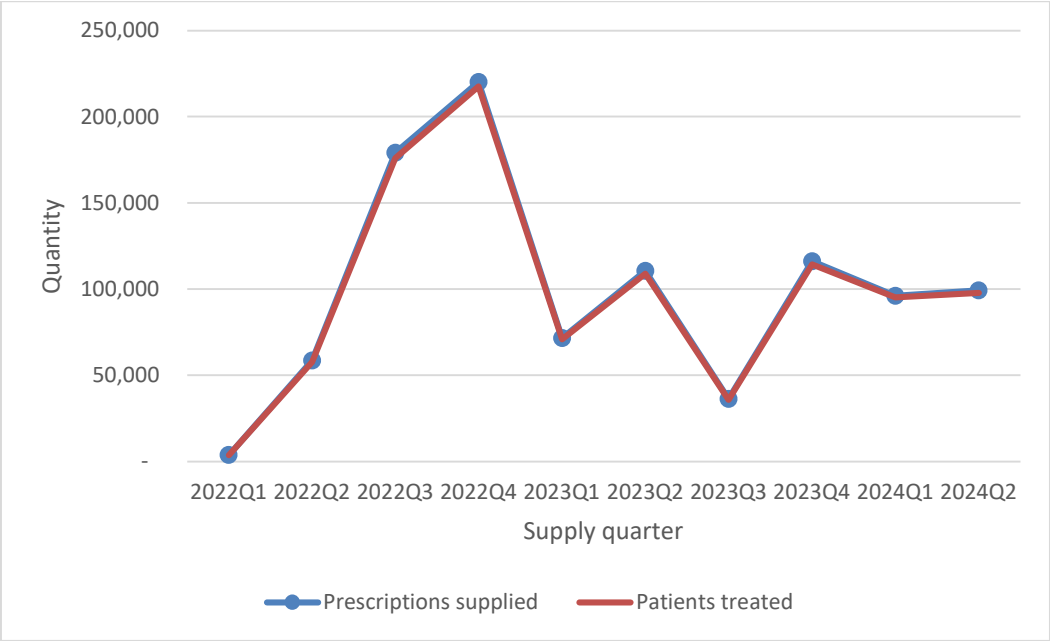

Figure 1: Utilisation of molnupiravir by supply quarter

Table 4 and Figure 1 shows utilisation of molnupiravir since PBS listing. Overall utilisation of molnupiravir had decreased, with lower utilisation in 2023 and 2024 compared to 2022.

Utilisation by relevant sub-populations/regions or patient level analysis

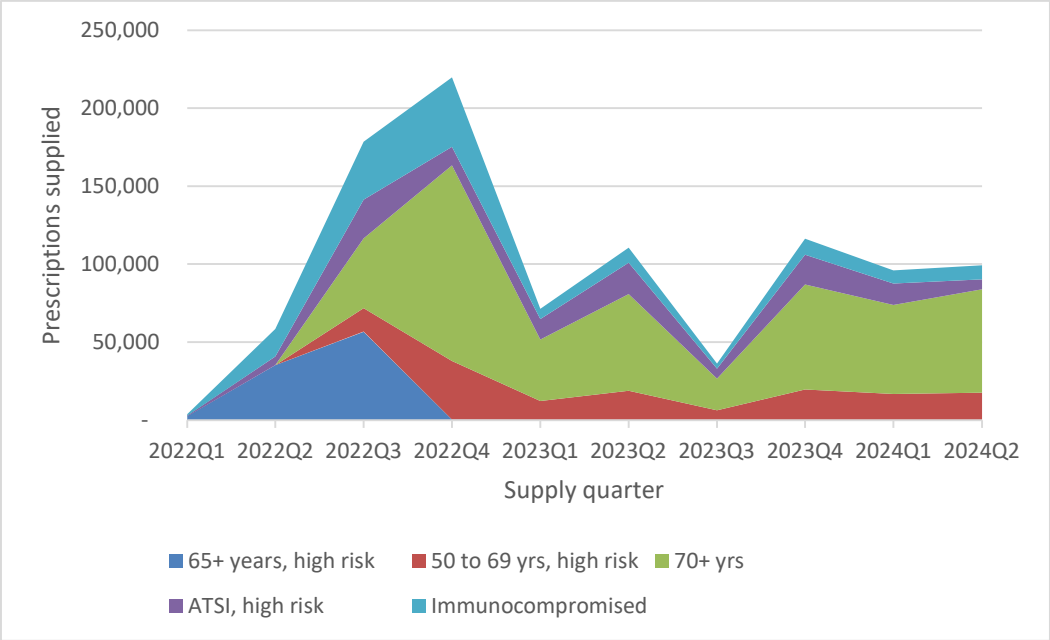

Figure 2: Molnupiravir prescriptions supplied by sub-population and supply quarter

Note: Less than one percent of molnupiravir prescriptions supplied had an unknown streamlined code and as such an unknown sub-population.

Figure 2 shows prescriptions supplied based on the sub-populations eligible for molnupiravir derived from the corresponding Streamlined code. From 2022Q2 onwards, most molnupiravir prescriptions supplied were for patients aged 70 years and over.

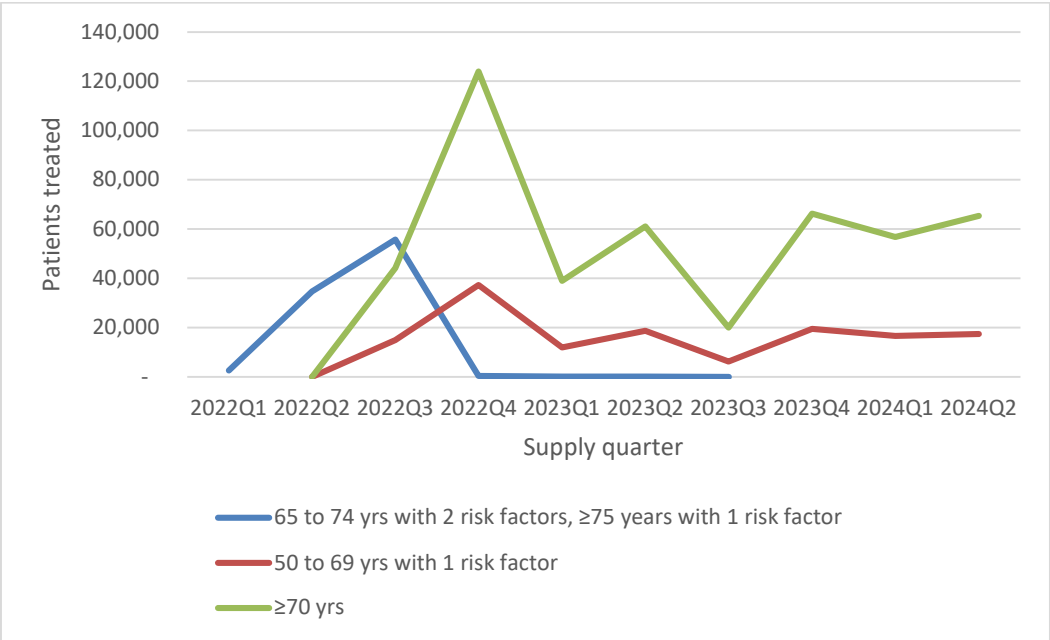

Figure 3: Molnupiravir treated patients by age group and supply quarter

Figure 3 shows the number of patients treated with molnupiravir by the age-related sub-populations. When molnupiravir was first PBS listed, treatment was restricted to patients aged 65-74 years with 2 risk factors or patients aged ≥75 years with 1 risk factor. When the sub-populations were extended, the patients aged 70 years and over accounted for the majority of utilisation.

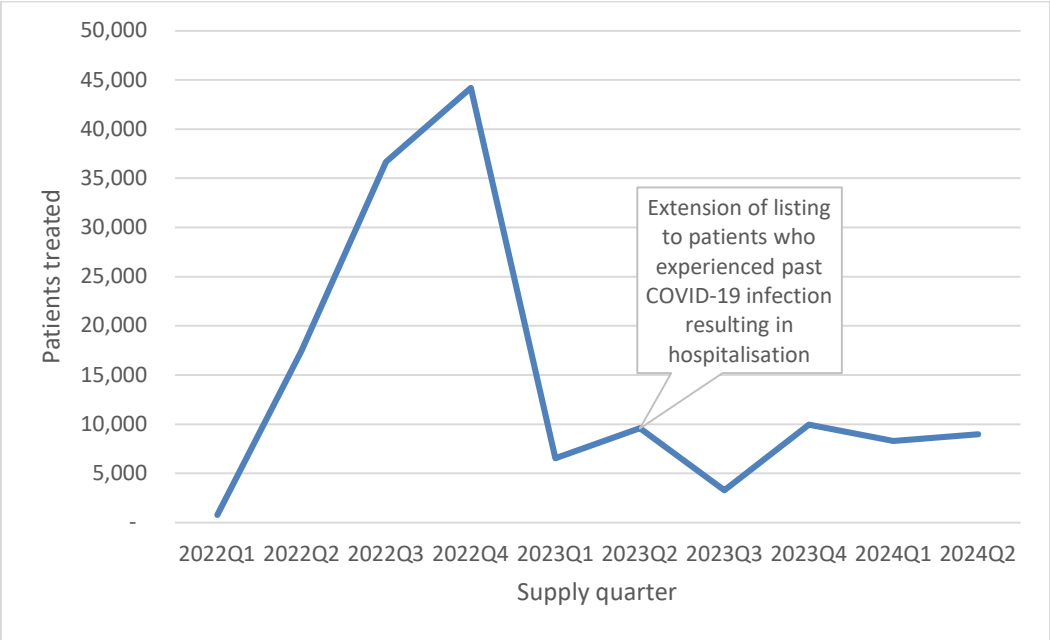

Figure 4: Immunocompromised patients or patients with past hospitalisation treated with molnupiravir by supply quarter

Figure 4 shows the number of moderately to severely immunocompromised patients aged 18 years and older and at risk of progression to severe disease. From February 2023 onwards, this sub-population was extended to include those aged 18 years and older who experienced past COVID-19 infection resulting in hospitalisation. The number of patients treated under this sub-population was greatest in 2022Q4.

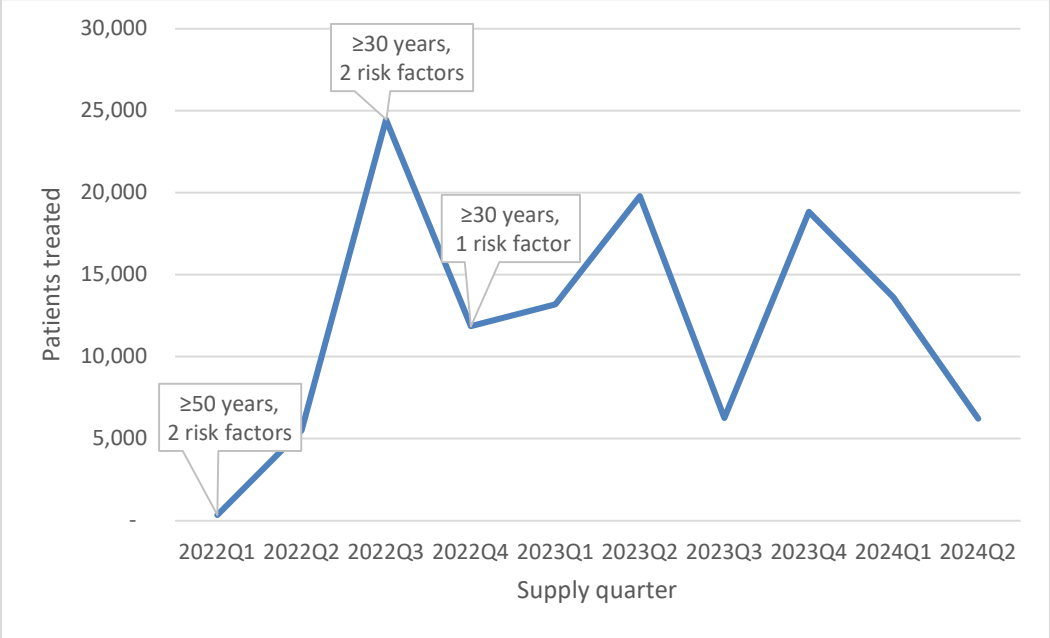

Figure 5: Aboriginal or Torres Strait Islander patients treated with molnupiravir by supply quarter

Figure 5 shows the number of Aboriginal or Torres Strait Islander patients treated with molnupiravir. Over time, this sub-population had extended its eligibility criteria, decreasing the eligible patient age from ≥50 years to ≥30 years and decreasing the number of risk factors from 2 to 1. As observed in the other sub-populations, the number of patients treated with molnupiravir was greatest in 2022. However, in 2023, there was a smaller percentage decrease in the number of patients treated with molnupiravir compared to the other sub-populations.

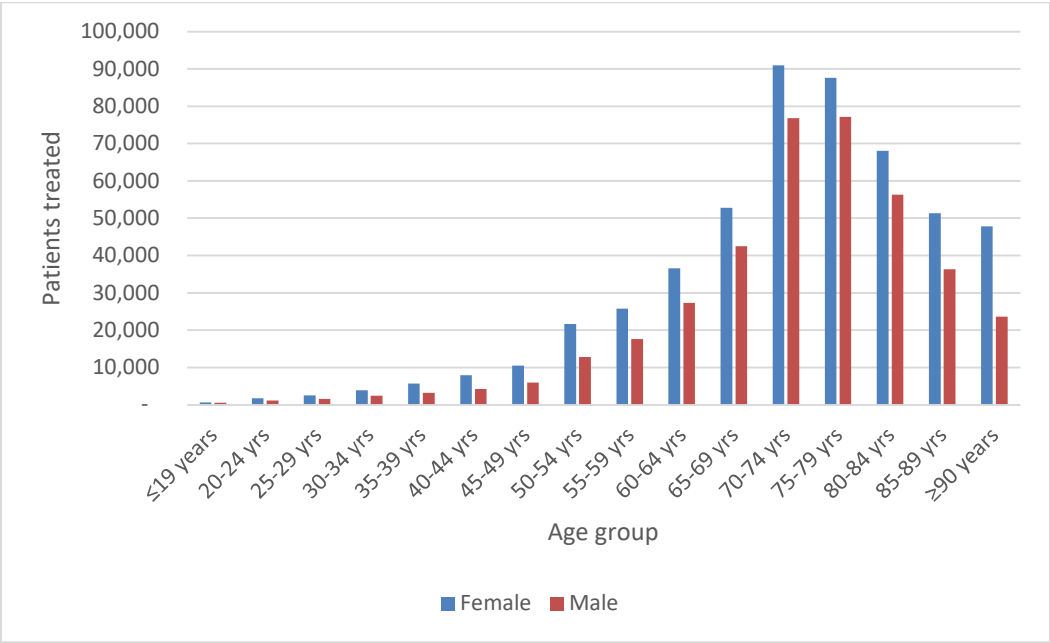

Figure 6: Age and gender distribution of molnupiravir patients in 2023

Figure 6 shows the age and gender distribution of molnupiravir patients in 2023. As shown in Figure 3, the majority of patients were aged 70 years and over. The most common age group were patients aged between 70 to 74 years. Females accounted for a greater proportion of utilisation across all age groups compared to males.

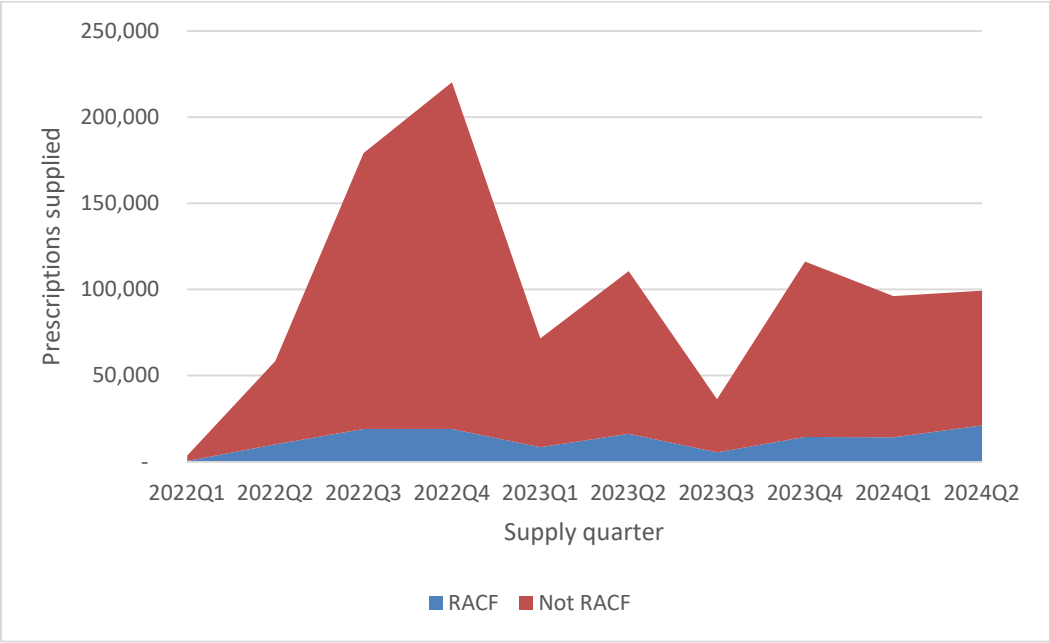

Figure 7: Molnupiravir prescriptions supplied by Residential Aged Care Facility (RACF) identifier and supply quarter

Figure 7 shows molnupiravir utilisation by residential aged care facility status. Patients treated with molnupiravir in RACFs accounted for approximately 16% of molnupiravir utilisation, with an average of 13,000 molnupiravir prescriptions per supply quarter.

It is noted as part of the National Medicines Stockpile (NMS), distribution of molnupiravir commenced on 6 February 2022 to all RACFs with outbreak sites prioritised for delivery. The NMS deployed 48,269 treatment courses of molnupiravir to RACFs.[6]

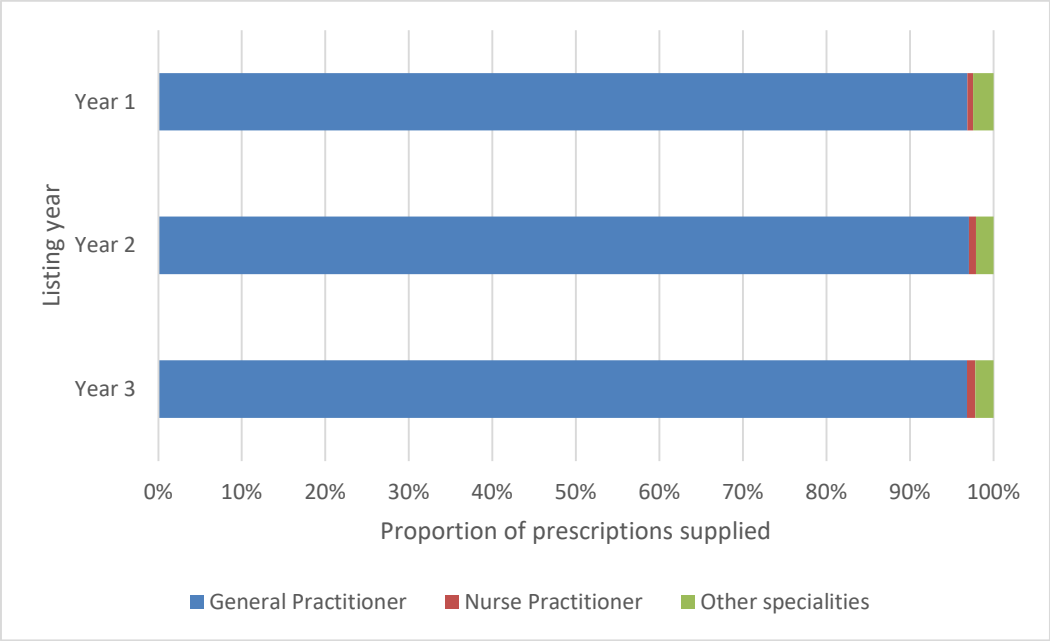

Figure 8: Molnupiravir prescriptions supplied by listing year and prescriber type

Figure 8 shows molnupiravir utilisation by prescriber type. General Practitioners accounted for at least 96% of molnupiravir prescriptions across all years.

[6] Australian Government Department of Health and Aged Care. COVID-19 outbreaks in Australian residential aged care facilities. Accessed from: https://www.health.gov.au/sites/default/files/2024-01/covid-19-outbreaks-in-australian-residential-aged-care-facilities-25-january-2024.pdf

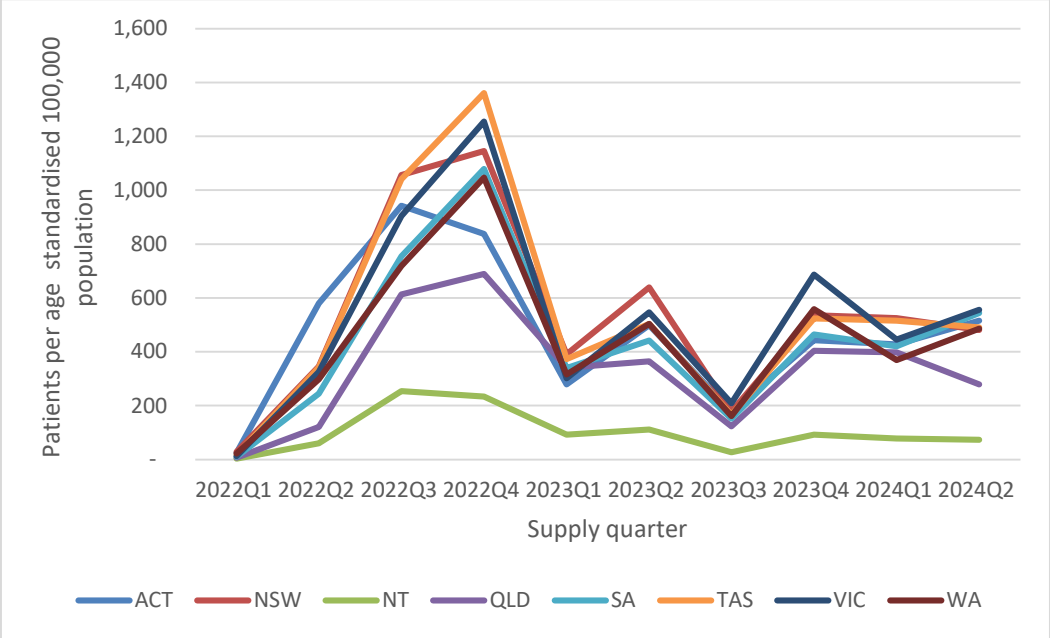

Figure 9: Molnupiravir treated patients by jurisdiction and supply quarter

Figure 9 shows the number of patients treated with molnupiravir standardised by each jurisdiction's population size over 18 years. Since PBS listing, the number of patients treated was the lowest in Northern Territory. The jurisdiction accounting for the highest molnupiravir utilisation has varied over time. Overall, all jurisdictions have had similar waves of utilisation over time.

Changes in the use of other drugs

Table 5: Utilisation of COVID-19 oral antivirals by calendar year

		2022	2023	2024
Patients treated	Molnupiravir	448,358	323,849	191,862
	Nirmatrelvir (&) ritonavir	160,630	226,760	131,863
Prescriptions supplied	Molnupiravir	466,598	356,307	206,883
	Nirmatrelvir (&) ritonavir	169,553	258,795	147,959

Note: Figures for 2022 and 2024 are not reflective of full calendar years. In 2022, molnupiravir prescriptions supplied is from March 2022 to December 2022 and for nirmatrelvir (&) ritonavir's figure is from May 2022 to December 2022. Figures in 2024 is from January 2024 to June 2024, inclusive.

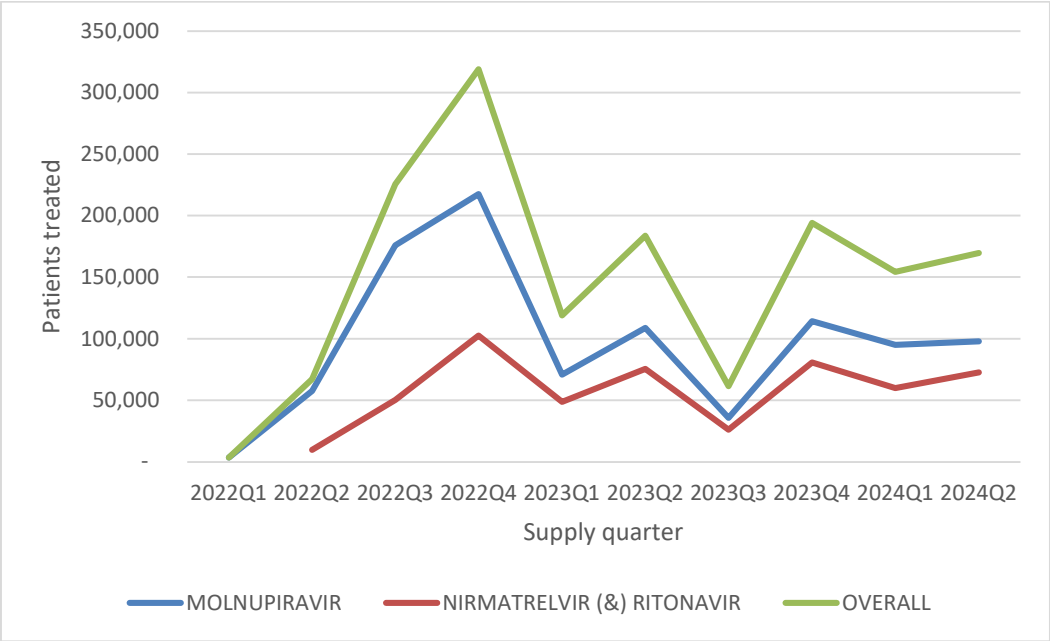

Figure 10: Patients treated with COVID-19 oral antivirals by supply quarter

Table 5 and Figure 10 shows utilisation of COVID-19 oral antivirals, with molnupiravir accounting for a greater proportion of utilisation compared to nirmatrelvir (&) ritonavir. Overall, both molnupiravir and nirmatrelvir (&) ritonavir appear to be following similar waves of utilisation, with peaks occurring mid- year and at the end of year.

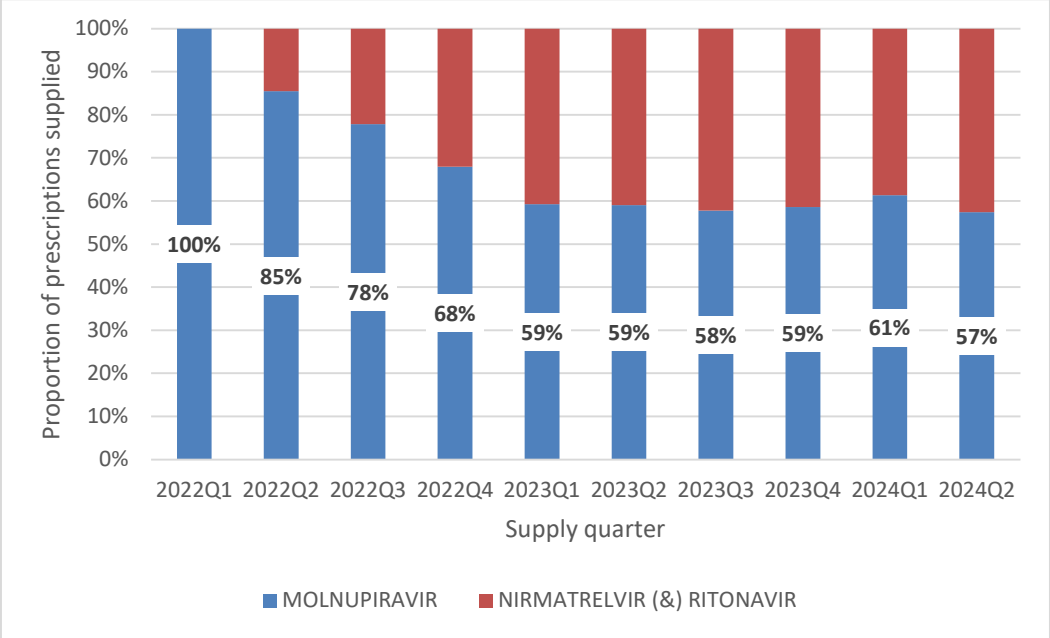

Figure 11: Market share of COVID-19 oral antivirals by supply quarter

Figure 11 shows the market share distribution of the COVID-19 antivirals, molnupiravir and nirmatrelvir and ritonavir. Although molnupiravir accounted for a greater proportion of the market share compared to nirmatrelvir (&) ritonavir since PBS listing, its market share had decreased over time.

Table 6: COVID-19 oral antiviral drug sequence prior to the formalisation of clinical criteria

SEQUENCE	PERCENTAGE
MOLNUPIRAVIR	64.9%
NIRMATRELVIR & RITONAVIR	32.5%
MOLNUPIRAVIR>NIRMATRELVIR & RITONAVIR	1.6%
NIRMATRELVIR & RITONAVIR>MOLNUPIRAVIR	0.9%
Other sequences	<0.1%

Table 6 shows the drug sequencing prior to the formalisation of the clinical criteria requiring patients treated with molnupiravir only when contraindicated to nirmatrelvir (&) ritonavir. The majority of patients received one supply of a COVID-19 oral antiviral, with most patients only being treated with molnupiravir.

Table 7: COVID-19 oral antiviral drug sequence following the formalisation of clinical criteria

SEQUENCE	PERCENTAGE
MOLNUPIRAVIR	57.6%
NIRMATRELVIR (&) RITONAVIR	41.9%
MOLNUPIRAVIR>NIRMATRELVIR (&) RITONAVIR	0.3%
NIRMATRELVIR (&) RITONAVIR>MOLNUPIRAVIR	0.2%
Other sequences	<0.1%

Table 7 shows following the formalisation of the clinical criteria in the restriction requiring molnupiravir treated patients to have a contraindication to nirmatrelvir (&) ritonavir, the proportion of patients treated with molnupiravir had decreased.

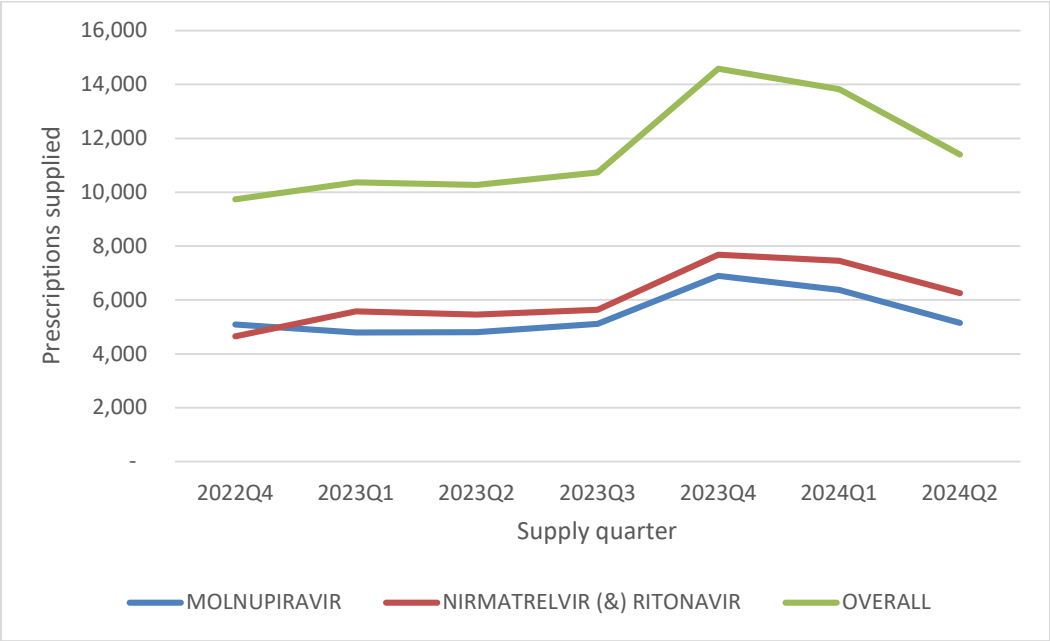

Figure 12: Utilisation of prescriber bag listings by drug and supply quarter

Figure 12 shows utilisation of Prescriber Bag COVID-19 oral antiviral listings. In contrast to utilisation trends observed in the General Schedule listings, a greater number of nirmatrelvir (&) ritonavir prescriptions were supplied compared to molnupiravir.

Discussion

Since its PBS listing, molnupiravir accounted for a greater proportion of the COVID-19 oral antiviral market share compared to nirmatrelvir and ritonavir (Figure 10). At its November 2023 meeting, 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 (paragraph 14.1, molnupiravir Public Summary Document, July 2023 with addendum November 2023).

The PBAC recommended the formalisation of the Administration Note into the clinical criterion and noted it is likely that it would take time to see the effect of the restriction change and over time this should reflect only patients strictly contraindicated for nirmatrelvir and ritonavir (approximately 15%, paragraph 13.28 molnupiravir Public Summary Document July 2023 with addendum November 2023). As shown in Figure 11, molnupiravir had a market share of approximately 57% since the formalisation of the clinical criterion. It was noted as part of the PBAC's consideration of molnupiravir in November 2023, the PBAC considered that the listing of molnupiravir be considered again in 3 years. The PBAC requested DUSC conduct a further review of oral antiviral utilisation for PBAC consideration in July 2026. At the time of this review, only three months of the data were available since the formalisation of the clinical criterion. Given that there would be 24 months of utilisation data following the formalisation of clinical criterion, further decreases in the market share of molnupiravir may be observed when the next DUSC review is undertaken.

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. The PBAC expected utilisation of the Prescriber Bag listings to be low (paragraph 14.4 molnupiravir Public Summary Document July 2023 with addendum November 2023). As shown above, utilisation of Prescriber Bag listings (Figure 12) were low relative to the General Schedule listings (Figure 10). In contrast to the General Schedule listings where a greater proportion of molnupiravir prescriptions were supplied, a greater proportion of nirmatrelvir and ritonavir prescriptions were supplied as part of the Prescriber Bag.

DUSC consideration

DUSC noted, molnupiravir currently had a TGA provisional approval 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. DUSC considered the potential QUM issues associated with prescribing a medicine under provisional approval given the potential safety risks. DUSC commented that prior to molnupiravir treatment, the patient should understand the potential safety risks noting that the Consumer Medicines Information (CMI) states "LAGEVRIO has provisional approval to treat COVID-19 in adults who are at increased risk for hospitalisation or death. The decision to approve this medicine has been made on the basis of results of data available at the time of provisional approval. More

evidence is required to be submitted when available to fully confirm the benefit and safety of LAGEVRIO for this use." DUSC noted the CMI states a number of points related to pregnancy and reproduction. The CMI states that treatment "is not recommended in pregnancy" and males who are sexually active with a partner who has the potential to become pregnant use a reliable method of contraception during treatment and for 3 months after the last dose of molnupiravir. DUSC considered whether patients were aware of the potential for teratogenicity. DUSC considered the potential for patients to have their drug regimen disrupted due to treatment with molnupiravir and considered whether these patients returned to their usual drug regimen following treatment.

DUSC noted that in addition to the PBS, the oral antivirals were supplied to patients through several channels including the National Medical Stockpile, the Aboriginal Community Controlled Health Organisation (ACCHO) and via State and Territory programs. DUSC noted that for the PBS listings there was a greater utilisation of molnupiravir compared to nirmatrelvir and ritonavir. DUSC commented that utilisation had not reflected the clinical evidence. DUSC noted this contrasted with utilisation of COVID-19 oral antivirals internationally, where there had been greater utilisation of nirmatrelvir and ritonavir compared to molnupiravir.[7] DUSC considered factors that may have contributed to the greater uptake of molnupiravir:

- As molnupiravir was the first COVID-19 oral antiviral to be placed in Residential Aged Care Facilities (RACF) through the National Medicines Stockpile, it became the preferred antiviral.
- The contraindications to nirmatrelvir and ritonavir which have changed over time, with limited guidance regarding its use initially and concern related to drug interactions.

DUSC considered the distribution and supply of medicines and lack of guidance regarding the safety of medicines during the COVID-19 pandemic and considered how future pandemics could be approached differently.

In contrast to the General Schedule listings, DUSC noted a greater proportion of nirmatrelvir and ritonavir prescriptions were supplied compared to molnupiravir as part of the Prescriber Bag. DUSC considered utilisation of the Prescriber Bag items may reflect the small proportion of clinicians who used these items in COVID-19 care centres and used nirmatrelvir with ritonavir based on best clinical practice.

DUSC noted the PBAC requested that the DUSC conduct a review of COVID-19 oral antiviral 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 DUSC review to support the PBAC consideration in July 2026. DUSC noted the PBAC undertook an expediated consideration of molnupiravir due to the urgent public health need to reduce hospitalisations and deaths associated with COVID-19 during the

[7] Murphy, S.J., Samson, L.W. and Sommers, B.D. COVID-19 Antivirals Utilization: Geographic and Demographic Patterns of Treatment in 2022. Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services. December 2022.

pandemic. DUSC noted molnupiravir was no longer subsidised in New Zealand from 1 February 2024.[8] DUSC noted the Pre-Sub-Committee Response (PSCR) statement that, "molnupiravir continues to be an important treatment choice for COVID-19, particularly for those aged over 70 years old, and those in Residential Aged Care who are contraindicated to nirmatrelvir-ritonavir. MSD looks forward to PBAC consideration of the real world effectiveness of molnupiravir and the DUSC review in July 2026".

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Merck Sharp & Dohme (Australia) Pty Ltd: The sponsor had no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any

[8] Pharmac Te Pataka Whaioranga. Molnupiravir access criteria. Accessed from: https://pharmac.govt.nz/news-and-resources/covid19/access-criteria-for-covid-19-medicines/molnupiravir

given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health and Aged Care has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, the Department of Health and Aged Care makes no warranties or representations as to accuracy or completeness of information contained in this report.

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Appendices

Appendix A: Risk factors and immunocompromised conditions listed in the molnupiravir PBS restriction (as at August 2024)

Population group	Immunocompromised conditions/risk factors
≥18 years old, moderately to severely immunocompromised and at risk of progression to severe disease OR experienced past COVID-19 infection resulting in hospitalisation	For the purpose of administering this restriction, 'moderately to severely immunocompromised' patients are those with: 1. Any primary or acquired immunodeficiency including: a. Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders, b. Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months), c. Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency; OR 2. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received: a. Chemotherapy or whole body radiotherapy, b. High-dose corticosteroids (at least 20 mg of prednisone per day, or equivalent) for at least 14 days in a month, or pulse corticosteroid therapy, c. Biological agents and other treatments that deplete or inhibit B cell or T cell function (abatacept, anti-CD20 antibodies, BTK inhibitors, JAK inhibitors, sphingosine 1-phosphate receptor modulators, anti-CD52 antibodies, anti-complement antibodies, anti-thymocyte globulin), 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 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 4. Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies; OR 5. People with disability with multiple comorbidities and/or frailty.

Population group	Immunocompromised conditions/risk factors
ATSI, ≥30 years old, 1 risk factor	1. The patient is in residential aged care 2. The patient has disability with multiple comorbidities and/or frailty 3. Neurological conditions, including stroke and dementia and demyelinating conditions 4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease 5. Heart failure, coronary artery disease, cardiomyopathies 6. Obesity (BMI greater than 30 kg/m^2) 7. Diabetes type I or II, requiring medication for glycaemic control 8. Renal impairment (eGFR less than 60mL/min) 9. Cirrhosis 10. The patient has reduced, or lack of, access to higher level healthcare and lives in an area of geographic remoteness classified by the Modified Monash Model as Category 5 or above 11. Past COVID-19 infection episode resulting in hospitalisation.
50-69 years old, 2 risk factors	1. The patient is in residential aged care, 2. The patient has disability with multiple comorbidities and/or frailty, 3. Neurological conditions, including stroke and dementia and demyelinating conditions, 4. Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease, 5. Heart failure, coronary artery disease, cardiomyopathies, 6. Obesity (BMI greater than 30 kg/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.