

5.05 RAXTOZINAMERAN, I.M. injection, suspension for injection containing raxtozinameran 30 micrograms, Comirnaty® Omicron XBB.1.5, Pfizer Australia Pty Ltd.

1 Purpose of submission

- 1.1 The Category 1 submission requested listing of raxtozinameran (also known as BNT162b2 XBB.1.5) on the National Immunisation Program (NIP) for the prevention of COVID-19 disease caused by the SARS-CoV-2 virus in adults aged ≥ 18 years at increased risk of severe COVID-19 disease.
- 1.2 This is the first submission to the Pharmaceutical Benefits Advisory Committee (PBAC) from any sponsor, seeking reimbursement of a vaccine for prevention of COVID-19.
- 1.3 In Australia, COVID-19 vaccines have been procured and funded under the National COVID-19 Vaccine Program (NCVP), rather than through the NIP. The Australian Government established this dedicated program at the outset of the pandemic to negotiate supply contracts, distribute vaccines nationwide, and cover all associated costs for eligible individuals. As noted in the cover letter provided with the submission, Pfizer currently supplies raxtozinameran (and also bretovameran) under an advance purchase agreement (APA). As also outlined in the cover letter, the rationale for the request for NIP listing of raxtozinameran was that the supply of COVID-19 vaccines under current arrangements is not unlimited or indefinite and planning for transition to ordinary non-APA supply is underway. The sponsor suggested that the transition of COVID-19 vaccines to the NIP is expected to commence in mid-2026. The PBAC noted that transition arrangements have not yet been confirmed.
- 1.4 The submission requested NIP listing for the 30 microgram dose of the vaccine, which is recommended for use in individuals aged 12 years and above. The submission did not request NIP listing for paediatric use. However, it suggested that NIP listing could be extended to the paediatric population who have severe immunocompromise or are at increased risk for severe COVID-19, based on clinical need in these children. Lower dose formulations are registered for paediatric populations (3 micrograms for children 6 months to 4 years, and 10 micrograms for children 5 to 11 years). The ESC considered it may not be feasible to move COVID-19 vaccinations from the NCVP to the NIP without providing access to the paediatric population.
- 1.5 The submission requested NIP listing for annual or biannual booster vaccinations for adults aged ≥ 18 years, as shown in Table 1. Listing was not proposed for primary vaccination. The ESC considered it was essential for any future NIP listing to provide eligibility for primary courses.

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- 1.6 Listing of raxtozinameran on the NIP was requested on the basis of a cost-effectiveness analysis versus no booster vaccination.
- 1.7 Table 1 summarises the key components of the clinical issue as specified by the submission.

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

Component	Description
Population	Adults at increased risk of COVID-19 including: <ul style="list-style-type: none"> Adults aged 18 to 64 years with increased risk of severe COVID-19 disease, including those with severe immunocompromise Adults aged ≥ 65 The PSCR clarified that NIP listing was also being sought for those aged 18-64 at standard risk of severe COVID-19.
Intervention ^a	Raxtozinameran 30 micrograms in 0.3 mL suspension administered by intramuscular injection as a booster vaccine against severe COVID-19 disease as follows: <ul style="list-style-type: none"> Adults aged 18 to 64 years with high risk of severe COVID-19: annual dose Adults aged 65 to 74 years with high risk of severe COVID-19: annual dose recommended but can consider biannual dose Adults aged 18 to 74 years with severe immunocompromise: biannual dose Adults ≥ 75 years: biannual dose The clinical evidence, economic evaluation and financial analyses presented in the submission also included adults aged 18-74 years who are not at high risk of severe acute COVID-19 (i.e., standard risk). The PSCR clarified that NIP listing was being sought for those aged 18-64 at standard risk of severe COVID-19.
Comparator	No (booster) vaccine Spikevax Omicron XBB.1.5 vaccine (andusomeran) was nominated as a near market comparator
Outcomes ^b	Incidence of severe COVID-19 Incidence of hospitalisation (including admission to ICU and/or ventilation) Mortality Vaccine efficacy for severe COVID-19, hospitalisation, and death
Clinical claim	In patients with a high risk of severe COVID-19, raxtozinameran is more effective than no (booster) vaccine in reducing the incidence of severe COVID-19, hospitalisation and mortality.

Source: Table 1.1.1 and Section 1 on pp12-32 of the submission

^a As detailed on p12 of the submission, the focus of the submission was on booster vaccinations given that the primary vaccination coverage rates in Australia are high (>92%) and an assumption that it is unlikely that the remaining unvaccinated adult population will seek a primary vaccination series, e.g., due to potential vaccine hesitancy.

^b The ATAGI pre-submission advice to PBAC (dated 29 August 2024) stated "ATAGI recommends that estimates of vaccine effectiveness should be limited to hospitalisations, intensive care admissions and death. Although data relating to vaccine efficacy in terms of COVID-19 cases may be derived from vaccine studies, the relevance of vaccine efficacy against asymptomatic disease is unclear. Furthermore, due to changes in the virus and methods of detection and reporting, the epidemiology of non-hospitalised COVID-19 will be less certain than hospitalised COVID-19. It is likely that there will be considerable uncertainty regarding the incidence of PACS (and case definition of PACS). ATAGI noted that clear evidence of the effect of the Comirnaty XBB.1.5 vaccine on the incidence of PACS that may arise following infection with currently circulating COVID-19 variants [would be] required [to support any claims in relation to PACS]."

COVID-19 = coronavirus 2019; PACS = post-acute COVID-19 syndrome

2 Background

Registration status

- 2.1 Raxtozinameran (Comirnaty® Omicron XBB.1.5) was TGA registered on 9 October 2023 for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 6 months of age and older.

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- 2.2 The Australian Public Assessment Report (AusPAR) for raxtozinameran reported that the evidentiary basis for the registration of raxtozinameran was limited to quality evaluation studies, non-clinical immunogenicity studies in mice, and a tissue distribution and spike protein expression study in mice. No clinical data were considered. At the time of registration, efficacy and safety was inferred from these data and from previous versions of the vaccine. Registration was based on acceptance that the known and potential benefits likely outweigh the known and potential risks with the updated vaccine, in consideration of the clinical need for the updated product. Clinical studies of safety, tolerability, and efficacy, as presented in the PBAC submission, became available after registration. This situation will also be relevant to future adaptations of the vaccine.
- 2.3 Brexovameran (Comirnaty® JN.1) was TGA registered on 11 October 2024 for the same indication. For illustration of the timeline, the application for brexovameran was submitted to the TGA on 28 June 2024, passed the TGA's preliminary assessment allowing it to proceed to TGA evaluation on 2 August 2024, and was registered on the ARTG approximately two months later on 11 October 2024. The ESC noted that the AusPAR for brexovameran had recently been published¹. As for raxtozinameran, no clinical data were considered. The TGA evaluation was limited to quality evaluation studies and non-clinical studies including immunogenicity studies in mice, and tissue distribution and spike protein expression studies in mice.

COVID-19 strain selection process

- 2.4 Since the beginning of the COVID-19 pandemic, numerous COVID-19 Variants of Concern (VOCs) and Variants of Interest (VOIs) have been designated by WHO based on their assessed potential for expansion and replacement of prior variants, for causing new waves with increased circulation, and for the need for adjustments to public health actions². The submission described the process in which expert committees of WHO, EMA and FDA conduct regular reviews of the latest epidemiology of COVID-19 and the impact of SARS-CoV-2 evolution on the performance of currently approved COVID-19 vaccines. Based on these reviews, the authorities make recommendations for the antigenic composition of future formulations of COVID-19 vaccines to enhance vaccine-induced immune responses to circulating SARS-CoV-2 variants.

TGA approval process for COVID-19 vaccines

- 2.5 The TGA approval process for COVID-19 vaccines was established to balance the clinical urgency for COVID-19 vaccines with scientific rigour. For adapted vaccines developed to address new variants, the process means that the TGA may approve

¹ <https://www.tga.gov.au/resources/auspar/comirnaty-jn1-covid-19-vaccine>, accessed 4 April 2025.

² <https://www.who.int/news/item/16-03-2023-statement-on-the-update-of-who-s-working-definitions-and-tracking-system-for-sars-cov-2-variants-of-concern-and-variants-of-interest>

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COVID-19 vaccines based, initially, on immunobridging studies before large-scale real-world effectiveness data are available. These studies compare immune responses (e.g., antibody levels) generated by a vaccine that is adapted to the circulating variant to a previously approved version of the vaccine. This approach is used when traditional efficacy trials are impractical, such as for variant-specific boosters or paediatric approvals. Sponsors are required to continue to review follow up clinical studies for safety analyses and submit updates to the TGA for patient information and drug safety as required. Pharmacovigilance data (i.e. PSUR/PBRER) are submitted regularly per requirements of the TGA.

- 2.6 In Australia, due to the active ingredient naming convention, strain update applications are required to be submitted as a Category 1 (type G) application (CAT 1G) or New Medicine Application (NMA), resulting in a new set of registrations/licenses upon approval. However, per the information published on the TGA website, the aim is to evaluate the application with a target timeframe equivalent to a minor variation (e.g. Category 3 application).
- 2.7 A summary of past TGA registrations of BNT162b2 (Comirnaty) vaccines is shown in Table 2, from the first registration of tozinameran (the original Comirnaty vaccine) in January 2021 through to approval of bretovameran (Comirnaty JN.1 vaccine) in October 2024.

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Table 2: History of registration of BNT162b2 vaccines in Australia

Chemical name Brand Name Approval status	Strength	Form	Age	ARTG Date
Tozinameran Comirnaty Initially provisional approval. Transitioned to full approval.	30 mcg/0.3 mL	multidose	≥12 years	25 Jan 21
	10 mcg/0.3 mL	multidose	5 to <12 years	6 Dec 21
	30 mcg/0.3 mL	multidose	≥12 years	6 Dec 21
	3 mcg/0.2 mL	multidose	6 months to < 5 yrs	30 Sep 22
Tozinameran/ riltozinameran Comirnaty Original/ Omicron BA.1 Provisional approval. Subsequently deregistered.	15 mcg/0.3 mL	multidose	≥18 years	28 Oct 22
Tozinameran/ famtozinameran Comirnaty Original/Omicron BA.4-5 Provisional approval ^a .	15 mcg/0.3 mL	multidose	≥12 years	23 Jan 23
	5 mcg/0.2 mL	multidose	5 to <12 years	21 Dec 23
	5 mcg/0.3 mL	single dose		21 Dec 23
	5 mcg/0.3 mL	multidose		21 Dec 23
	15 mcg/0.3 mL	single dose	≥12 years	21 Dec 23
Raxtozinameran Comirnaty Omicron XBB.1.5 Full approval	10 mcg/0.3 mL	multidose	5 to <12 years	9 Oct 23
	30 mcg/0.3 mL	multidose	≥12 years	9 Oct 23
	3 mcg/0.2 mL	multidose	6 months to <5 yrs	22 Dec 23
	3 mcg/0.3 mL			22 Dec 23
	10 mcg/0.2 mL	multidose	5 to <12 years	22 Dec 23
	10 mcg/0.3 mL	single dose		22 Dec 23
	30 mcg/0.3 mL	single dose	≥12 years	22 Dec 23
	30 mcg/0.3 mL	Prefilled glass syringe	≥12 years	12 Aug 24
	30 mcg/0.3 mL	Prefilled plastic syringe	≥12 years	12 Aug 24
Bretovameran Comirnaty JN.1 Full approval	10 mcg/0.3 mL	multidose	5 to <12 years	11 Oct 24
	30 mcg/0.3 mL	multidose	≥12 years	11 Oct 24
	3 mcg/0.2 mL	multidose	6 months to <5 yrs	11 Oct 24
	3 mcg/0.3 mL			11 Oct 24
	10 mcg/0.2 mL	multidose	5 to <12 years	11 Oct 24
	10 mcg/0.3 mL	single dose		11 Oct 24
	30 mcg/0.3 mL	single dose	≥12 years	11 Oct 24
	30 mcg/0.3 mL	Prefilled glass syringe	≥12 years	11 Oct 24
30 mcg/0.3 mL	Prefilled plastic syringe	≥12 years	11 Oct 24	

Source: Table 1.3.1 of the submission.

a. For the tozinameran/famtozinameran combination vaccine, the submission stated that transition to full approval was planned for end 2024, however that did not occur. On 19 November 2024, the TGA extended the provisional registration period to 20 January 2027 as reported on the TGA website, <https://www.tga.gov.au/resources/artg/400874>, accessed 4 April 2025.

ATAGI advice

2.8 The ATAGI provided pre-submission advice to the PBAC for this submission, dated 29 August 2024. The advice stated that the ATAGI's preferred scenario for NIP listing was based on the current ATAGI recommendations, prioritising populations at increased risk for severe disease. The submission noted this advice, however also stated that clinical evidence for raxtozinameran to support NIP listing for paediatric patients was not available. Current ATAGI advice (at the time of PBAC consideration) indicated that children and adolescents aged 5 to 17 years with severe immunocompromise are eligible to receive a COVID-19 vaccine every 12 months. The

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submission presented clinical evidence for raxtozinameran in adult populations and requested NIP listing for adults.

- 2.9 The submission proposed populations and schedules based on current ATAGI recommendations for booster doses for adults (February 2024)³. The recommended populations were unchanged in the updated advice published in the ATAGI statement on the administration of COVID-19 vaccines in 2025⁴.
- 2.10 In regard to primary courses, the submission's assumption that the remaining unvaccinated adult population would not seek a primary vaccination series fails to consider that patients who were previously not eligible can become eligible e.g., due to advancing age, and does not consider that current recommendations allow more than a single dose as a primary course for adults with severe immunocompromise. This is discussed further in paragraphs 3.5 and 3.6.
- 2.11 In regard to variant-adapted COVID-19 vaccines: The submission sought NIP listing for Comirnaty Omicron XBB.1.5 vaccine (which contains raxtozinameran, also known as BNT162b2 XBB.1.5). This was consistent with ATAGI's pre-submission advice (August 2024) which indicated that the most relevant clinical evidence is with the latest adaptation of the BNT162b2 vaccine against the latest circulating variants, which was noted to be BNT162b2 XBB.1.5 vaccine for the prevention of the currently circulating variants, XBB.1.5 and JN.1. Raxtozinameran was manufactured for the 2023-2024 Northern Hemisphere fall and winter season. As discussed in paragraph 2.3, a more recent vaccine was registered by the TGA in October 2024, called Comirnaty JN.1 vaccine (which contains bretovameran, also known as BNT162b2 JN.1).
- 2.12 Additional advice was sought from the ATAGI in relation to questions arising from the evaluation and provided to the sponsor with the ESC advice.
- 2.13 The ESC noted that ATAGI will continue to monitor both epidemiology of COVID-19, and international evidence of effectiveness and safety of new vaccine strains. Accordingly, the ATAGI may consider changes to its advice in future if there are signs that the severity of the disease, transmissibility of the virus, vaccine effectiveness, or vaccine safety have altered.

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

³ ATAGI statement on the administration of COVID-19 vaccines in 2024, Issue date: 29 February 2024. <https://www.health.gov.au/resources/publications/atagi-statement-on-the-administration-of-covid-19-vaccines-in-2024?language=en>

⁴ ATAGI statement on the administration of COVID-19 vaccines in 2025, Issue date: 27 March 2025. <https://www.health.gov.au/resources/publications/atagi-statement-on-the-administration-of-covid-19-vaccines-in-2025?language=en>

3 Requested listing

3.1 The proposed NIP listing for raxtozinameran is shown below. The listing would allow either annual or biannual doses of vaccine depending on the individual’s age and risk status. The AIH definitions at the time of the evaluation are shown for 1) Conditions which increase the risk of severe COVID-19 disease; and 2) Severely immunocompromising conditions for which additional doses of COVID-19 vaccine are recommended. Definitions provided in the AIH would be used in practice to determine eligibility for annual or biannual doses. Some updates were made to the AIH definitions on 2 May 2025⁵ (not shown).

Vaccine and the circumstances in which vaccine may be provided	Brand	Dose	Formulation	Requested price per dose	Number and timing of doses																		
Vaccine Raxtozinameran (BNT162b2 XBB.1.5) COVID-19 vaccine	Comirnaty® Omicron XBB.1.5	0.3 mL	Injection (0.3 mL)	\$ [REDACTED]	1 or 2 doses per year (depending on age and risk status)																		
<p><u>Circumstances:</u></p> <p>Booster vaccinations for the following groups (annual or biannual dosing schedule based on the ATAGI statements on the administration of COVID-19 vaccines in 2024 and 2025):</p> <ol style="list-style-type: none"> 1. Persons aged 18-64 years: <table style="width: 100%; border: none;"> <tr> <td style="padding-left: 20px;">A) At standard risk of severe acute COVID-19 (SR)</td> <td style="text-align: right;">annual^a</td> </tr> <tr> <td style="padding-left: 20px;">B) At high risk of severe acute COVID-19 (HR)</td> <td style="text-align: right;">annual</td> </tr> <tr> <td style="padding-left: 20px;">C) With severe immunocompromise (IC)</td> <td style="text-align: right;">biannual</td> </tr> </table> 2. Persons aged 65-74 years: <table style="width: 100%; border: none;"> <tr> <td style="padding-left: 20px;">D) At standard risk of severe acute COVID-19 (SR)</td> <td style="text-align: right;">biannual^b</td> </tr> <tr> <td style="padding-left: 20px;">E) At high risk of severe acute COVID-19 (HR)</td> <td style="text-align: right;">biannual</td> </tr> <tr> <td style="padding-left: 20px;">F) With severe immunocompromise (IC)</td> <td style="text-align: right;">biannual</td> </tr> </table> 3. Persons aged 75 years or more at any risk of severe acute COVID-19 (AR), which includes: <table style="width: 100%; border: none;"> <tr> <td style="padding-left: 20px;">G) At standard risk of severe acute COVID-19 (SR)</td> <td style="text-align: right;">biannual</td> </tr> <tr> <td style="padding-left: 20px;">H) At high risk of severe acute COVID-19 (HR)</td> <td style="text-align: right;">biannual</td> </tr> <tr> <td style="padding-left: 20px;">I) With severe immunocompromise (IC)</td> <td style="text-align: right;">biannual</td> </tr> </table> <p>Duration of listing: ongoing NIP cohort</p>						A) At standard risk of severe acute COVID-19 (SR)	annual ^a	B) At high risk of severe acute COVID-19 (HR)	annual	C) With severe immunocompromise (IC)	biannual	D) At standard risk of severe acute COVID-19 (SR)	biannual ^b	E) At high risk of severe acute COVID-19 (HR)	biannual	F) With severe immunocompromise (IC)	biannual	G) At standard risk of severe acute COVID-19 (SR)	biannual	H) At high risk of severe acute COVID-19 (HR)	biannual	I) With severe immunocompromise (IC)	biannual
A) At standard risk of severe acute COVID-19 (SR)	annual ^a																						
B) At high risk of severe acute COVID-19 (HR)	annual																						
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D) At standard risk of severe acute COVID-19 (SR)	biannual ^b																						
E) At high risk of severe acute COVID-19 (HR)	biannual																						
F) With severe immunocompromise (IC)	biannual																						
G) At standard risk of severe acute COVID-19 (SR)	biannual																						
H) At high risk of severe acute COVID-19 (HR)	biannual																						
I) With severe immunocompromise (IC)	biannual																						
<p>Conditions which increase the risk of severe COVID-19 disease (as stated in the Australian Immunisation Handbook)^c</p> <p>This list is not exhaustive, and providers should use their judgement to vaccinate people with conditions not listed.</p> <ul style="list-style-type: none"> • Immunocompromising condition - due to disease or treatment 		<p>Severely immunocompromising conditions for which additional doses of COVID-19 vaccine are recommended (as stated in the Australian Immunisation Handbook)^d</p> <p>The example conditions and therapies listed are not exhaustive, and providers may include conditions or therapies similar to those below based on clinical judgement.</p> <ul style="list-style-type: none"> • Haematological malignancies (treated and untreated) <ul style="list-style-type: none"> ○ Leukaemia 																					

⁵ <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/covid-19>, accessed 9 May 2025.

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<ul style="list-style-type: none"> ○ Asplenia ○ Splenic dysfunction ○ HIV infection ○ Solid organ transplant ○ Haematopoietic stem cell transplant • Cardiac disease <ul style="list-style-type: none"> ○ Congenital heart disease ○ Congestive heart failure ○ Coronary artery disease • Chronic respiratory disease <ul style="list-style-type: none"> ○ Severe asthma ○ Cystic fibrosis ○ Bronchiectasis ○ Suppurative lung disease ○ Chronic obstructive pulmonary disease ○ Chronic emphysema • Chronic neurological condition <ul style="list-style-type: none"> ○ Hereditary and degenerative CNS disease ○ Seizure disorder ○ Spinal cord injury ○ Neuromuscular disorder ○ Condition which increases respiratory infection risk • Chronic metabolic condition <ul style="list-style-type: none"> ○ Type 1 or 2 diabetes ○ Amino acid disorder ○ Carbohydrate disorder ○ Cholesterol biosynthesis disorder ○ Fatty acid oxidation defect ○ Lactic acidosis ○ Mitochondrial disorder ○ Organic acid disorder ○ Urea cycle disorder ○ Vitamin/cofactor disorder ○ Porphyria • Chronic kidney disease (stage 4 or 5) • Haematologic disorder <ul style="list-style-type: none"> ○ Haemoglobinopathy • Chronic liver disease <ul style="list-style-type: none"> ○ Cirrhosis ○ Autoimmune hepatitis ○ Non-alcohol fatty liver disease ○ Alcoholic liver disease • Chromosomal abnormality <ul style="list-style-type: none"> ○ Trisomy 21 • Obesity, body mass index ≥ 30 kg per m² 	<ul style="list-style-type: none"> ○ Lymphoma ○ Other lymphoproliferative disorder ○ Plasma cell dyscrasia • Malignancy, solid organ transplantation, autoimmune, and inflammatory conditions currently treated with <ul style="list-style-type: none"> ○ haematopoietic stem cell transplant or CAR-T therapy within the last 24 months ○ conventional chemotherapy ○ conventional immunosuppressive agent at significant doses, e.g.: <ul style="list-style-type: none"> • ≥ 20 mg/day of prednisone for ≥ 14 days in a month • high dose methotrexate ≥ 20 mg per week • azathioprine ≥ 3.0 mg/kg/day • 6-mercaptopurine ≥ 1.5 mg/kg/day • mycophenolate ≥ 1 g/day • tacrolimus and other systemic calcineurin inhibitors • sirolimus and other mTOR inhibitors • cyclophosphamide ○ rituximab or other B-cell, and T-cell, targeted monoclonal antibody ○ JAK inhibitor or other small molecule targeted therapy ○ fingolimod or other immunomodulatory drugs ○ eculizumab ○ monotherapy with infliximab or other anti-TNF Alpha monoclonal antibody or anakinra, tocilizumab or other anti-interleukin monoclonal antibody are not considered severely immunocompromising for the purposes of COVID-19 vaccine recommendations • HIV with CD4+ cell count < 200 • Inborn errors of immunity (primary immunodeficiency) <ul style="list-style-type: none"> ○ Severe Combined immunodeficiency (SCID), other combined disorders, humoral, phagocytic disorders, complement defects • chronic kidney disease on dialysis
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Source: Compiled during the evaluation and amended to reflect clarifications in PSCR.

Abbreviations: AR = all risk; HR = high risk; IC = immunocompromised; SR = standard risk.

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- a. The PSCR clarified that NIP listing was being sought for those aged 18-64 at standard risk of severe COVID-19.
 - b. Consistent with the ATAGI statements on the administration of COVID-19 vaccines in 2024 and 2025, the submission stated that this group can be considered for COVID-19 vaccinations every six months. However the economic model and financial estimates inappropriately assumed that no patients in the 65-74-year-old SR group would receive biannual doses (see paragraph 6.81).
 - c. Australian Immunisation Handbook. Conditions for which COVID-19 vaccination can be considered: <https://immunisationhandbook.health.gov.au/recommendations/adults-aged-18-years-are-recommended-to-receive-covid-19-vaccine>, accessed 14 March 2025. The list of conditions was subsequently updated (see paragraph 3.1).
 - d. Australian Immunisation Handbook. Severely immunocompromising conditions for which additional doses of COVID-19 vaccine are recommended: <https://immunisationhandbook.health.gov.au/recommendations/people-with-severe-immunocompromise-are-recommended-to-receive-covid-19-vaccine>, accessed 14 March 2025. The list of conditions was subsequently updated (see paragraph 3.1).
- 3.2 The requested price per 30 mcg dose of raxtozinameran proposed in the submission was \$ [REDACTED] per dose.
- 3.3 The AIH recommendations for COVID-19 vaccination are shown in Table 3. As can be seen in Table 3, the proposed listing of raxtozinameran on the NIP (shaded in grey) was not fully aligned with the current eligibility criteria for raxtozinameran on the NCVP and as recommended by ATAGI. The proposed listing of raxtozinameran on the NIP was substantially narrower than the current listing on the NCVP meaning there would be gaps in comparison with current arrangements. The two most significant gaps were primary courses, and paediatric doses. In relation to unvaccinated pregnant women, the AIH recommendation to includes the recommendation to receive a primary dose of COVID-19 vaccine, which can be given at any time during pregnancy, noting that unvaccinated pregnant women are at increased risk of severe disease and adverse perinatal outcomes from COVID-19.
- 3.4 The Pre-Sub-Committee Response (PSCR) proposed that a pragmatic approach could be taken by the PBAC for the populations that were not covered by the submission, however the ESC noted that the submission did not include corresponding economic or financial analyses to support PBAC consideration for these populations. The ESC considered that it would have been more appropriate for the submission to have sought NIP listing that was consistent with ATAGI recommendations as specified in the AIH including paediatric formulations, and primary courses, such that a resulting recommendation for NIP listing would include all relevant vaccines, doses and circumstances of use. This would have included a request for primary immunisation and for children who are immunocompromised.

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Table 3: ATAGI recommendations for vaccination with XBB.1.5 or JN.1-based COVID-19 vaccines with populations for whom NIP listing of raxtozinameran was requested shaded in grey (updated 2 May 2025)^a

Age	Characteristics	Primary (one course per lifetime)	Booster (per year)
6 months to < 5 years	Standard risk	nil	nil
	Medical risk condition without severe immunocompromise	Consider 2 doses	Not recommended
	Severe immunocompromise	Consider 2-3 doses	Not recommended
5 to < 18 years	Standard risk	nil	nil
	Medical risk condition without severe immunocompromise	Consider 1 dose	Not recommended
	Severe immunocompromise	Consider 1-2 doses	Consider 12 monthly boosters
18 to 64 years	Standard risk	1 primary dose	Consider 12 monthly boosters
	Medical risk condition without severe immunocompromise	1 primary dose	Consider 12 monthly boosters
	Severe immunocompromise	2 primary doses, consider a third	Recommended 12 monthly boosters, consider 6 monthly boosters
65 to 74 years	Standard risk	1 primary dose	Recommended 12 monthly boosters, consider 6 monthly boosters
	Medical risk condition without severe immunocompromise	1 primary dose	Recommended 12 monthly boosters, consider 6 monthly boosters
	Severe immunocompromise	2 primary doses, consider a third	Recommended 12 monthly boosters, consider 6 monthly boosters
Older than 75 years	Standard risk	1 primary dose	Recommended 6 monthly boosters
	Medical risk condition without severe immunocompromise	1 primary dose	Recommended 6 monthly boosters
	Severe immunocompromise	2 primary doses, consider a third	Recommended 6 monthly boosters
Pregnant women	Unvaccinated	1 primary dose any time during pregnancy	As per non-pregnant people

a. The submission requested NIP listing for adults (30 microgram dose). Lower dose formulations are registered for paediatric populations (3 micrograms for children 6 months to 4 years, and 10 micrograms for children 5 to 11 years).

Grey shading indicates that vaccination of this group was requested by the current submission.

Source: Australian Immunisation Handbook, updated 2 May 2025 ⁶, The term "Standard risk" is not used in AIH, but is used here to reflect ATAGI advice for patients within the age group that are not considered high risk, or severely immunocompromised.

3.5 The submission noted that the focus of the submission was on booster vaccinations given that the primary vaccination coverage rates in Australia are high (>92%) and an assumption that the remaining unvaccinated adult population would be unlikely to seek a primary vaccination series, e.g., due to vaccine hesitancy. The assumption that the remaining unvaccinated adult population would not seek a primary vaccination series fails to consider that patients who were previously not eligible can become eligible e.g., due to advancing age.

3.6 The Australian Immunisation Handbook⁷ states:

⁶ <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/covid-19>

⁷ Recommendations | COVID-19 | The Australian Immunisation Handbook, last updated 22 November 2024, available at <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/covid-19#recommendations>. Last accessed 14 March 2025.

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- Primary course vaccination is recommended for all people aged 18 years or older with medical conditions that may increase their risk of severe disease or death from COVID-19.
- Most people require 1 dose for their primary course. People with severe immunocompromise are recommended 2 primary doses and can consider a 3rd.
- Further doses every 6 or 12 months are recommended (i.e. booster doses), or can be considered, based on an individual's age and presence of risk factors for severe disease.

In summary, while most of the adult cohorts are recommended to receive a single dose as a primary course, which could be achieved with the submission's proposed schedule which is silent on whether a vaccine is a first dose (primary) or subsequent dose (booster), some of the adult population is recommended to receive up to 3 doses as a primary course.

- 3.7 The submission noted that the ATAGI pre-submission advice to PBAC (29 August 2024) indicated that Aboriginal and Torres Strait Islander people are at higher risk of severe COVID-19 and mortality due to a higher prevalence of comorbidities that increase the risk of severe COVID-19 than the general Australian population. Currently, it is recommended that Aboriginal and Torres Strait Islanders receive COVID-19 vaccine (primary course with or without booster), depending on their age, immune status, and whether they have the conditions listed in the Australian Immunisation Handbook that are considered to increase their risk of severe COVID-19. The submission considered the advice for this population was fairly consistent with other individuals at high risk of severe COVID-19 and did not request any additional NIP eligibility criteria for broader access for Aboriginal and Torres Strait Islanders. The evaluation considered this was consistent with the current advice.
- 3.8 As detailed in Table 4 below, there were inconsistencies across the submission regarding the assumed number of doses per year in the various populations. For example, the submission proposed 'biannual' dosing for adults aged 18-64 years with severe immunocompromise but 'annual or biannual' dosing for adults aged 65-74 years with severe immunocompromise. ATAGI recommendations are currently identical for these two populations (i.e., recommended every 12 months but can consider a dose every 6 months). Some changes to the assumed utilisation were proposed in the PSCR as noted in Table 4.

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Table 4: ATAGI recommendations for booster COVID-19 vaccination (as was applicable in February 2024) and assumed utilisation of raxtozinameran doses on the NIP as described in the submission

Age group	Risk category	Doses per year as per ATAGI recommendation (inconsistent see footnote ^c)	Doses per year in submission Section 3 with assumed proportions of use	Doses per year in submission Section 4 with assumed proportions of use
18 – 64 years	Standard	0 or 1 based on a risk-benefit assessment ^a	0.07%: 1 (revised in PSCR ^d) Remainder: 0	0.07%: 1 Remainder: 0
	High ^a		50%: 1 Remainder: 0	50%: 1 Remainder: 0
	IC ^b	1 or 2	100%: 1 (inappropriately revised from 2 to 1 in PSCR ^e) Remainder: 0	100%: 1 (inappropriately excludes estimate for 2 doses)
65 – 74 years	Standard	1 or 2	18.87%: 1 Remainder: 0 (inappropriately excludes estimate for 2 doses)	18.87%: 1 Remainder: 0 (inappropriately excludes estimate for 2 doses)
	High ^a		80%: 1 (inappropriately revised from 2 to 1 dose, in PSCR ^f) Remainder: 0	80%: 1 Remainder: 0 (inappropriately excludes estimate for 2 doses)
	IC ^b	1 or 2	100%: 2 (revised in PSCR ^g) Remainder: 0	100%: 2
≥ 75 years	Standard	2	49.36%: 2 ^h Remainder: 0	28.62%: 2 Remainder: 0
	High ^a		49.36%: 2 ^h Remainder: 0	80%: 2 Remainder: 0
	IC ^b		49.36%: 2 ^h Remainder: 0	100%: 2

Source: Table 1.2.1 on p38 and Sections 3 and 4 of the submission; ATAGI recommendation

IC = immunocompromised; NIP = National Immunisation Program

a Adults with risk conditions may be at increased risk of severe COVID-19 as described in AIH.

b Severely immunocompromising conditions as described in AIH.

c The ATAGI recommendations in this column were not consistently applied in the economic model and financial estimates.

d The submission economic model applied an uptake of 0.07% in the SR population aged 18-64, which did not match the financial estimates which calculated uptake of 0.07% for this population. The PSCR clarified that 0.07% was the intended value to apply in both the economic model and financial estimates.

e. The submission economic model applied an uptake of 90% for biannual dosing in the IC population aged 18-64, which did not match the financial estimates which applied uptake of 100% annual for this population. The PSCR clarified that 100% annual dosing was intended to apply in both the economic model and financial estimates. However, this does not reflect ATAGI advice for this group.

f. The submission economic model applied an uptake of 80% in the HR population aged 65-74, which matched the financial estimates in terms of proportion but did not match in terms of dosing regimen. The economic model assumed biannual doses, consistent with ATAGI advice, but the financial estimates assumed only annual doses. The PSCR clarified that the inputs should be 80% for annual dosing, and remainder 0, as shown above, and this would match the financial estimates. However, this does not reflect ATAGI advice for this group.

g. The submission economic model applied an uptake of 90% in the IC population aged 65-74, which did not match the financial estimates which applied uptake of 100% for this population. The PSCR clarified that 100% was the intended value to apply in both the economic model and financial estimates.

h. For the 75+ age group, the submission model applied a weighted average uptake of 49.36%. This was derived from an uptake of 28.62% in the SR group, 80% in the HR group and 100% in the IC group, which matched the financial estimates.

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

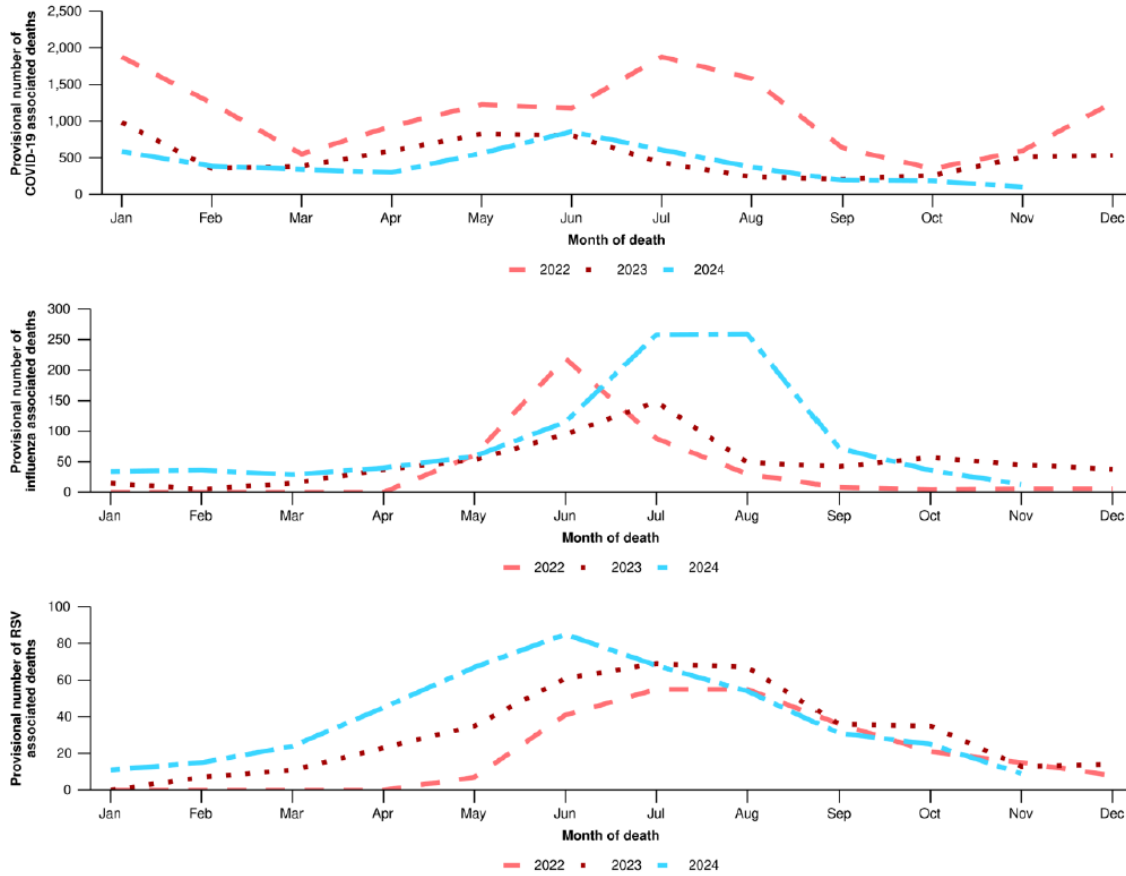
4 Population and disease

- 4.1 COVID-19 is an infectious disease caused by SARS-CoV-2, an enveloped positive-sense single-stranded genomic RNA virus belonging to the Coronaviridae family of viruses. It was first reported in December 2019 in Wuhan, China, and soon after, the virus and the disease spread across the globe.
- 4.2 The primary mode of transmission of SARS-CoV-2 is person to person via respiratory droplets which infect mucosal surfaces (e.g., nose, mouth and eyes).
- 4.3 The severity of COVID-19 ranges from asymptomatic to critical illness.
- 4.4 Mortality from COVID-19 in Australia has been significant. The AIHW report, Australia's Health 2024, identified COVID-19 as one of the top 5 leading causes of mortality in Australia in 2022. The Australian Respiratory Surveillance Report – 30 December to 26 January 2025⁸ reported that COVID-19 was the leading cause of acute respiratory infection mortality across 2022 – 2024. Figure 1 presents the number of deaths due to COVID-19, influenza and respiratory syncytial virus (RSV) in 2022, 2023 and 2024 (note that the scale of the y-axes vary across the graphs).

⁸ <https://www.health.gov.au/sites/default/files/2025-01/australian-respiratory-surveillance-report-30-december-2024-to-26-january-2025.pdf> [Last accessed: 7 Feb 2025]

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Figure 1: Provisional numbers of acute respiratory infection-associated deaths^{a,b,c} by month, year and respiratory infection, Australia, 2022 – November 2024



Source: Table 15, Australian Respiratory Surveillance Report – 30 December 2024 to 26 January 2025.

a An acute respiratory-associated death is one where the viral disease has either directly caused the death or the person has died with the virus (a person has died from another cause but the viral illness still contributed significantly to death). Includes acute respiratory disease death registrations only.

b Data is provisional and subject to change. It can take several weeks for death registrations to be reported, processed, coded, validated, and tabulated. Therefore, the data shown here may be incomplete, and will likely not include all deaths that occurred during a given time. Data includes all deaths (both doctor and coroner-certified) that occurred and were registered by 30 November 2024. Please refer to the Technical Supplement for more information.

c All deaths involving COVID-19 in this report have been coded to ICD-10 codes U07.1-U07.2, U10.9 or U09.9. All deaths involving influenza have been coded to J09-J11. All deaths involving RSV have been coded to J12.1, J20.5, J21.0, B97.4.

4.5 Older individuals (>60 years old) and those with underlying health conditions (e.g., diabetes, cardiac disease, pulmonary disease, immunosuppression) have a greater risk of developing severe or critical disease⁹. COVID-19 vaccination status and history of natural infection with SARS-CoV-2 or other endemic coronaviruses also affect the risk of developing severe or critical disease.

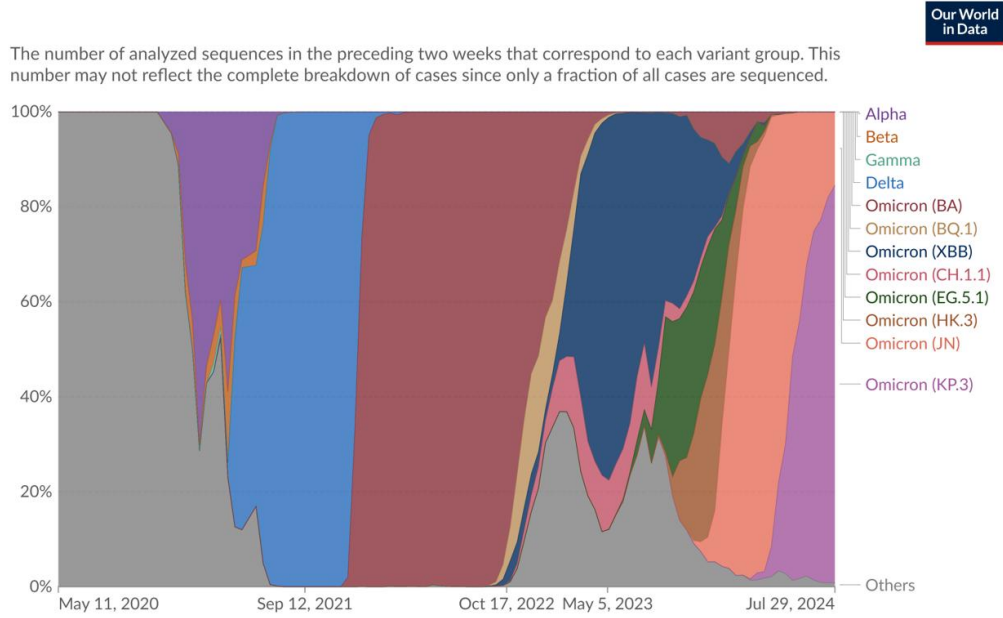
4.6 Long COVID (sometimes referred to as ‘post-acute sequelae of COVID-19’ [PACS] or post-COVID condition) is a condition where patients experience a broad range of

⁹ <https://www.who.int/docs/default-source/ncds/un-interagency-task-force-on-ncds/uniatf-policy-brief-ncds-and-covid-030920-poster.pdf>

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Australian Respiratory Surveillance Report (Report 17, 2024)¹² stated that, in the reporting period from 18 November 2024 to 15 December 2024, the JN.1 sub-lineage remained the dominant circulating sub-lineage. The KP.3 sub-sub-lineage was the most common JN.1 sub-lineage recorded in AusTrakka. It also reported that there had been an increasing proportion of the recombinant lineage XEC sequenced. The ESC noted Australian Respiratory Surveillance Report – 27 January to 23 March 2025¹³ reports that the recombinant lineage XEC and sublineages of the JN.1 variant are now the dominant SARS-CoV-2 variants circulating in Australia, as shown in Figure 4. On 24 January 2025, the World Health Organization (WHO) designated LP.8.1 as a variant under monitoring. The WHO have not yet released a risk evaluation for LP.8.1. The data shown in Figure 3 and Figure 4 highlight that the pattern of evolution with SARS-CoV-2 can be rapid and remains unpredictable.

Figure 3: SARS-CoV-2 variants in analysed sequences, Australia



Data source: GISAID, via CoVariants.org (2024) OurWorldinData.org/coronavirus | CC BY
 Note: Recently-discovered or actively-monitored variants may be overrepresented, as suspected cases of these variants are likely to be sequenced preferentially or faster than other cases.

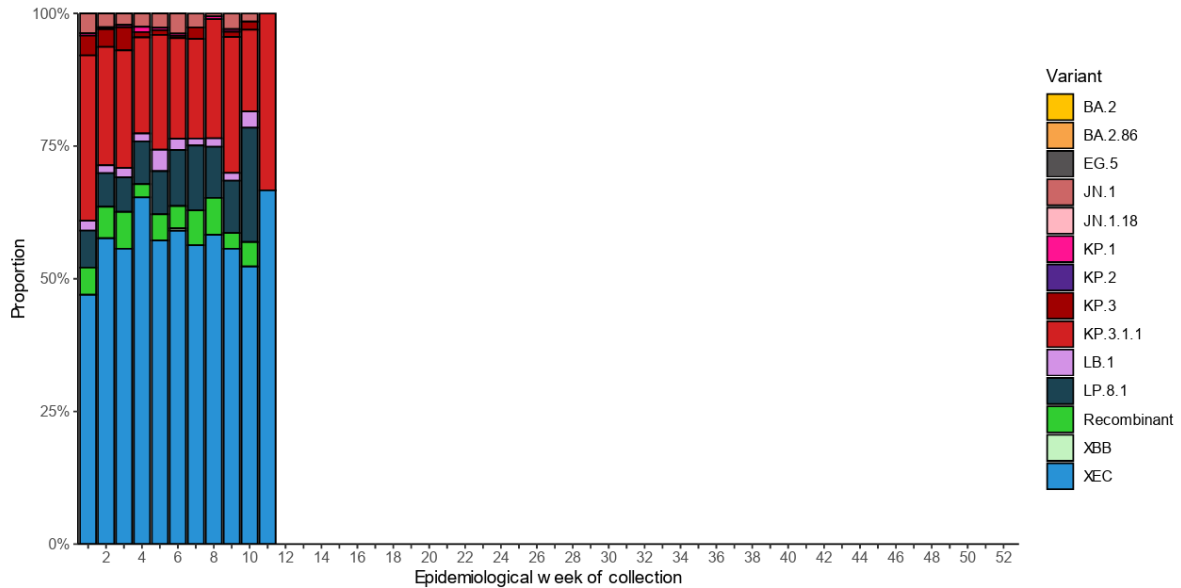
Source: Figure 1.1.1 on p 17 of the submission

¹² <https://www.health.gov.au/sites/default/files/2024-12/australian-respiratory-surveillance-report-17-18-november-to-15-december-2024.pdf>

¹³ <https://www.health.gov.au/sites/default/files/2025-03/australian-respiratory-surveillance-report-24-february-to-23-march-2025.pdf> [Last accessed: 7 Apr 2025]

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Figure 4: SARS-CoV-2 Omicron sub-lineage^a sequences by sample collection date, showing the count of sequences per week^{b,c}, Australia, 1 January to 23 March 2025



Source: Figure 17.a of the Australian Respiratory Surveillance Report – 27 January to 23 February 2025

^a Some sub-sub-lineages are shown alongside their parent lineage but not included in the parent lineage totals. For instance, KP.2 and KP.3 are sub-sub lineages of JN.1, so the total of JN.1 sequences will be higher than shown in the corresponding colour alone, and should include the KP.2 and KP.3 totals.

^b Sequences in AusTrakka aggregated by week and reported based on date of sample collection, not date of sequencing.

^c Data for earlier weeks may change between reporting periods as sequences with older collection dates are uploaded. These numbers are not equivalent to number of cases, as there are many cases which may not be sequenced. Non-VOI (variants of interest) and non-VUM (variants under monitoring) Omicron sub-lineages have been collapsed into parent lineages BA.1, BA.2, BA.3, BA.4 and BA.5.

4.9 BNT162b2 is an mRNA vaccine, a nucleoside-modified mRNA-based vaccine that encodes the SARS-CoV-2 spike protein (S). The role of S is to mediate binding and fusion of the virus to host cell receptors, allowing the virus to enter host cells and replicate. S is a key target of neutralising antibodies and therefore an important antigen for vaccine development.

4.10 The original monovalent Comirnaty[®] COVID-19 vaccine, also known as BNT162b2 (and tozinameran) was developed for the prevention of COVID-19 caused by the ancestral (Wuhan) strain of SARS-CoV-2 which was first identified in Australia in early 2021. Pivotal RCTs for the BNT162b2 platform such as Study C459001 for the primary

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course¹⁴ and Study C4591031 for a third dose¹⁵ were described in appendices to the submission.

- 4.11 The evolution of variants of the virus over time has prompted adaptations of the original BNT162B2 vaccine so that the nucleoside-modified RNA encoding the viral spike protein was adapted to match the prevailing strains of SARS-CoV-2.
- 4.12 The submission described that vaccines that are better matched to currently circulating variants offer enhanced protection against symptomatic and severe disease, and that vaccines matched to previous variants offer significantly reduced protection against severe COVID-19 outcomes, given the significant viral mutations occurring as the virus adapts and evades immunity provided by prior infection or prior vaccination, emphasising the need to maintain a close match of the COVID-19 vaccine to the circulating variants.
- 4.13 Raxtozinameran, the subject of this submission, is the BNT162b2 vaccine matched to the XBB.1.5 SARS-CoV-2 variant.
- 4.14 Bretovameran is the BNT162b2 vaccine matched to the JN.1 SARS-CoV-2 variant and was registered by the TGA in October 2024. Current ATAGI advice recommends JN.1 vaccines.
- 4.15 Although there may be an ongoing need for booster vaccination of people at high risk of severe COVID-19, changes in the circulating SARS-CoV-2 variants mean that the need for boosters is not static and the need for a particular booster (in this case, raxtozinameran) may change over time e.g., due to changes in transmissibility or pathogenicity of SARS-CoV-2. For example, the Omicron variants of SARS-CoV-2 have been associated with lower hospitalisation rates and mortality compared to the Delta variant (independent of previous immunity), which may support limiting availability of COVID-19 vaccines to those at high risk of severe COVID-19 but, if the circulating variant becomes more pathogenic, then the populations for whom the vaccine is recommended may require expansion.
- 4.16 The ESC advised that, given the changes in circulating variants in Australia, there was no place in therapy for the monovalent raxtozinameran vaccine. Raxtozinameran is an

¹⁴ Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.

¹⁵ Moreira ED Jr, Kitchin N, Xu X, Dychter SS, Lockhart S, Gurtman A, Perez JL, Zerbini C, Dever ME, Jennings TW, Brandon DM, Cannon KD, Koren MJ, Denham DS, Berhe M, Fitz-Patrick D, Hammitt LL, Klein NP, Nell H, Keep G, Wang X, Koury K, Swanson KA, Cooper D, Lu C, Türeci Ö, Lagkadinou E, Tresnan DB, Dormitzer PR, Şahin U, Gruber WC, Jansen KU; C4591031 Clinical Trial Group. Safety and Efficacy of a Third Dose of BNT162b2 Covid-19 Vaccine. *N Engl J Med.* 2022 May 19;386(20):1910-1921. doi: 10.1056/NEJMoa2200674. Epub 2022 Mar 23. PMID: 35320659; PMCID: PMC9006787.

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XBB.1.5-adapted vaccine and the current scenario is that the XBB.1.5 variant of SARS-CoV-2 is no longer circulating. The predominant circulating variants are related to the JN.1 variant of SARS-CoV-2.

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

5 Comparator

- 5.1 The submission nominated no booster vaccine as the main comparator and nominated Spikevax® XBB.1.5 (andusomeran) as a near-market comparator, which was approved by the TGA in October 2023.
- 5.2 The PBAC considered the appropriate main comparator was no booster vaccination given that no COVID-19 vaccines are currently included on the NIP.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (2) via the Consumer Comments facility on the PBS website.
- 6.3 The input from the individual did not support the vaccine. The input stated that vaccination was neither necessary nor effective to prevent COVID-19.
- 6.4 The comments from organisations were supportive of the proposed NIP listing of raxtozinameran. Some of the main themes of the input were:
 - Lung Foundation Australia highlighted additional risks of COVID-19 for Australians living with lung diseases including increased risk of symptom exacerbation, lung function deterioration, hospitalisation and even death. The input noted that post-acute sequelae may develop after acute COVID-19 and discussed key risk factors including recurrent COVID-19 infections and not being vaccinated. The Foundation stated it is vital that COVID-19 vaccinations are freely available, particularly among those most at risk of associated harm such as older adults, pregnant people, and people with an underlying health condition such as a lung disease. High-level results from a survey of 3,352 adults living in Australia, which found that more than half (53%) of respondents living with lung disease were very worried about contracting a respiratory infection, compared to 19% of respondents not living with lung disease.
 - National Aboriginal Community Controlled Health Organisation (NACCHO) noted that identification as Aboriginal or Torres Strait Islander is not a risk factor in itself

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but must be understood within the broader context of systemic inequities that impact health. The input stated that ensuring continued access to this vaccine is critical in addressing these disparities and protecting the wellbeing of Aboriginal and Torres Strait Islander individuals, families, and communities. NACCHO described additional considerations for meeting the needs of Aboriginal and Torres Strait Islander people in relation to access to antiviral treatments. There are currently two PBS-funded oral antiviral medications for COVID-19, Lagevrio (molnupiravir) and Paxlovid (nirmatrelvir + ritonavir), however these treatments must be started within five days of symptom onset, which can be challenging for Aboriginal and Torres Strait Islander people, particularly those in rural and remote areas, due to systemic and geographic barriers to timely healthcare. NACCHO highlighted that given these challenges, vaccination remains a crucial preventive measure, reducing the risk of severe disease, hospitalisation, and long COVID symptoms while also decreasing reliance on antiviral treatments that may not always be accessible. It was noted that seven COVID-19 vaccines are currently available in Australia, all are manufactured by Pfizer. NACCHO noted that a single-dose pre-filled syringe (PFS) formulation, offers potential advantages over single and multi-dose vial preparations, such as reduced preparation time, increased ease of use, and reduced wastage. The input stated that the PFS formulation can enhance clinician confidence in vaccine administration, supporting more consistent and efficient delivery in remote communities.

Clinical studies

- 6.5 The submission presented 32 reports relating to 25 individual studies that investigated the efficacy of XBB.1.5-adapted mRNA vaccine, as listed in Table 5.
- 6.6 The PSCR asserted that “the evidence presented to the PBAC for raxtozinameran (XBB.1.5) provides comprehensive and extensive evidence for decision making on the BNT162b2 platform. With that, raxtozinameran is the most appropriate proxy for any future TGA approved BNT162b2 vaccine at the time of NIP listing and thereafter, to provide adequate protection to Australians from the circulating variants as identified by advisory group (e.g. ATAGI) and expert committees of WHO, EMA and FDA.”
- 6.7 The addendum to the pre-PBAC response provided an overview of the BNT162b2 vaccine RCTs and real-world evidence studies, based on information provided in the appendices to the sponsor’s PBAC submission.

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Table 5: Studies and associated reports presented in the submission

Study	Title
C4591054 substudies	<p>A phase 2/3 protocol to investigate the safety, tolerability, and immunogenicity of BNT162b2 RNA-based vaccine candidates for SARS-CoV-2 new variants in healthy individuals.</p> <p><u>Substudy A</u> was conducted in in two groups of participants: participants aged 12 – 55 years and participants aged > 55 years. Participants in this substudy were required to have received ≥ 3 prior doses of an mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5-adapted bivalent vaccine ≥ 150 days prior to vaccination with raxtozinameran in the substudy.</p> <p><u>Substudy B</u> was conducted in participants aged > 12 years who were previously exposed to SARS-CoV-2 and were COVID-19 vaccine-naïve. Participants received raxtozinameran.</p> <p><u>Another substudy</u> investigated the immunogenicity and safety of bretoivameran in healthy adult individuals. Participants could be COVID-19 vaccine naïve or experienced (with any number of prior doses of any COVID-19 vaccine) but could not have received a COVID-19 vaccine < 150 days before vaccination with bretoivameran in the substudy.</p> <p>Publications:</p> <p>Gayed J., Diya O., et al. Safety and immunogenicity of the monovalent Omicron XBB.1.5-adapted BNT162b2 COVID-19 vaccine in individuals ≥12 years old: a phase 2/3 trial. <i>Vaccines</i>. 2024;12(2):118. https://doi.org/10.3390/vaccines12020118</p> <p>Gayed J., Bangad V., et al. Immunogenicity of the monovalent Omicron XBB.1.5-adapted BNT162b2 COVID-19 vaccine against XBB.1.5, BA.2.86, and JN.1 sublineages: A Phase 2/3 trial. <i>Vaccines</i>. 2024;12(7):734. https://doi.org/10.3390/vaccines12070734</p> <p>Diya O., Gayed J., et al. A phase 2/3 trial to investigate the safety and immunogenicity of monovalent Omicron JN.1-adapted BNT162b2 COVID-19 vaccine in adults ≥18 years old. 2024. Preprint. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4976664</p>
Andersson 2024*	<p>Andersson N.W., Thiesson E.M., et al. Comparative effectiveness of monovalent XBB.1.5 containing COVID-19 mRNA vaccines in Denmark, Finland, and Sweden: target trial emulation based on registry data. <i>BMJ Medicine</i>. 2024;3:e001074 https://bmjmedicine.bmj.com/content/3/1/e001074</p>
Antunes 2024	<p>Antunes L., Mazagatoz C., et al. Early COVID-19 XBB.1.5 vaccine effectiveness against hospitalisation among adults targeted for vaccination, VEBIS Hospital Network, Europe, October 2023–January 2024. <i>Influenza and Other Respiratory Viruses</i>, 2024;18(8):e13360. https://doi.org/10.1111/irv.13360</p>
Caffrey 2024*	<p>Caffrey A.R., Appaneal H.J., et al. Effectiveness of BNT162b2 XBB vaccine in the US Veterans Affairs Healthcare System. <i>Nature Communications</i>. 2024;15(1):9490. https://doi.org/10.1038/s41467-024-53842-w</p>
Chong 2024	<p>Chong C., Wee L.E., et al. Risks of SARS-CoV-2 JN.1 infection and COVID-19-associated emergency department visits/hospitalizations following updated boosters and prior infection: a population-based cohort study. <i>Clinical Infectious Diseases</i>. 2024;79(5):1190-1196. https://doi.org/10.1093/cid/ciae339</p>
DeCuir 2024	<p>DeCuir J., Payne A.B., et al. Interim effectiveness of updated 2023-2024 (monovalent XBB.1.5) COVID-19 vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalization among immunocompetent adults aged ≥ 18 years - VISION and IVY Networks, September 2023-January 2024. <i>MMWR. Morbidity and Mortality Weekly Report</i>. 2024;73(8):180-188. https://doi.org/10.15585/mmwr.mm7308a5</p>
Delaunay 2024	<p>Laniece Delaunay C., Melo A., et al. Effectiveness of COVID-19 vaccines administered in the 2023 autumnal campaigns in Europe: Results from the VEBIS primary care test-negative design study, September 2023-January 2024. <i>Vaccine</i>. 2024;42(19):3931-3937. https://doi.org/10.1016/j.vaccine.2024.05.067</p>
Hansen 2024	<p>Hansen C.H., Moustsen-Helms I.R., et al. Short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study. <i>Lancet. Infectious Diseases</i>, 2024;24(2):e73-e74. https://doi.org/10.1016/s1473-3099(23)00746-6</p>
Huiberts 2024	<p>Huiberts A.J., Hoever C.E., et al. Effectiveness of Omicron XBB.1.5 vaccine against infection with SARS-CoV-2 Omicron XBB and JN/1 variants, prospective cohort study, the Netherlands, October 2023 to January 2024. <i>Euro Surveillance (European communicable disease bulletin)</i>. 2024;29(10):2400109. https://doi.org/10.2807/1560-7917.es.2024.29.10.2400109</p>

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Study	Title
Kirsebom 2024	Kirsebom F.C.M., Stowe J., et al. Effectiveness of autumn 2023 COVID-19 vaccination and residual protection of prior doses against hospitalisation in England, estimated using a test-negative case-control study. <i>Journal of Infection</i> . 2024;89(1):106177. https://doi.org/10.1016/j.jinf.2024.106177
Lin 2024a*	Lin D.Y., Du Y., et al. Effectiveness of XBB.1.5 vaccines against Omicron subvariants. <i>Medical Research Archives</i> . 2024;12(8). https://doi.org/10.18103/mra.v12i8.5740
Lin 2024b	Lin D.Y., Du Y., et al. Durability of XBB.1.5 vaccines across Omicron subvariants. <i>New England Journal of Medicine</i> 2024;390(22):2124-2127. https://doi.org/10.1056/NEJMc2402779
Link-Gelles 2024a	Link-Gelles R., Ciesla A.A., et al. Early Estimates of Updated 2023-2024 (Monovalent XBB.1.5) COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection attributable to co-circulating Omicron variants among immunocompetent adults - Increasing community access to testing program, United States, September 2023–January 2024. <i>MMWR. Morbidity and Mortality Weekly Report</i> . 2024;73(4):77-83. https://doi.org/10.15585/mmwr.mm7304a2
Link-Gelles 2024b	Link-Gelles R. Vaccine effectiveness of updated (2023-2024) COVID-19 vaccines. Presentation to the Advisory Committee on Immunization Practices meeting, 28-29 Feb 2024, Atlanta, GA https://stacks.cdc.gov/view/cdc/148495
Link-Gelles 2024c	Link-Gelles R., Effectiveness of COVID-19 (2023-2024 formula) vaccines. Presentation to the Advisory Committee on Immunization Practices meeting. 26-28 Jun 2024, Atlanta, GA. https://stacks.cdc.gov/view/cdc/157891
Liu 2024	Liu B., Scaria A., et al. Effectiveness of XBB.1.5 monovalent COVID-19 vaccine against COVID-19 mortality in Australians aged 65 years and older during August 2023 to February 2024. medRxiv preprint: https://doi.org/10.1101/2024.08.12.24311895 ; this version posted August 13, 2024
Monge 2024	Monge S., Humphreys J., et al. Effectiveness of XBB.1.5 monovalent COVID-19 vaccines during a period of XBB.1.5 dominance in EU/EEA countries, October to November 2023: A VEBIS-EHR Network Study. <i>Influenza and Other Respiratory Viruses</i> . 2024;18(4):e13292. https://doi.org/10.1111/irv.13292
Moustsen-Helms 2024	Moustsen-Helms I.R., Bager P., et al, for the SSI-DMC study group. Relative vaccine protection, disease severity, and symptoms associated with the SARS-CoV-2 omicron subvariant BA.2.86 and descendant JN.1 in Denmark: a nationwide observational study. <i>Lancet. Infectious Diseases</i> . 2024;24(9):964-973. https://doi.org/10.1111/irv.13292
Nguyen 2024*	Nguyen J.L., Mitratza M., et al. Effectiveness of the BNT162b2 XBB.1.5-adapted vaccine against COVID-19 hospitalization related to the JN.1 variant in Europe: A test-negative case-control study using the id.DRIVE platform. <i>EClinicalMedicine</i> . 2024;79:102995 https://doi.org/10.1016/j.eclinm.2024.102995
Nham 2024	Nham E., Sohn J.W., et al. Effectiveness of COVID-19 XBB.1.5 monovalent mRNA vaccine in Korea: interim analysis. <i>Frontiers in Immunology</i> . 2024;15:1382944. https://doi.org/10.3389/fimmu.2024.1382944
Nunes 2024*	Nunes B., Humphreys J., et al. Monovalent XBB.1.5 COVID-19 vaccine effectiveness against hospitalisations and deaths during the Omicron BA.2.86/JN.1 period among older adults in seven European countries: A VEBIS-EHR Network Study. <i>Expert Review of Vaccines</i> . 2024;23(1):1085-1090. https://doi.org/10.1080/14760584.2024.2428800
Shrestha 2024a	Shrestha N.K., Burke P.C. et al. Effectiveness of the 2023–2024 formulation of the COVID-19 messenger RNA vaccine. <i>Clinical Infectious Diseases</i> ., 2024;79(2):405–11. https://doi.org/10.1093/cid/ciae132
Shrestha 2024b	Shrestha N.K., Burke P.C., et al. Effectiveness of the 2023–2024 formulation of the coronavirus disease 2019 mRNA vaccine against the JN.1 variant. medRxiv preprint. https://doi.org/10.1101/2024.04.27.24306378 ; this version posted May 20, 2024.
Tartof 2023	Tartof S.Y., Slezak J.M., et al. BNT162b2 XBB1.5-adapted vaccine and COVID-19 hospital admissions and ambulatory visits in US adults. medRxiv, preprint. https://www.medrxiv.org/content/10.1101/2023.12.24.23300512v1 ; this version posted Dec 28, 2023. The analyses presented in this paper appear to have been refined, peer-reviewed and published in the report labelled Tartof 2024b.
Tartof 2024a	Tartof S.Y., Slezak J.M., Effectiveness of BNT162b2 XBB vaccine against XBB and JN.1 sub-lineages. medRxiv, preprint. https://www.medrxiv.org/content/10.1101/2024.05.04.24306875v1

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Study	Title
Tartof 2024b	The analyses presented in this paper appear to have been refined, peer reviewed and published and is in the report labelled Tartof 2024c. Tartof S.Y., Slezak J.M., et al. Estimated effectiveness of the BNT162b2 XBB vaccine against COVID-19. JAMA Internal Medicine. 2024;184(8):932-940. https://doi.org/10.1001/jamainternmed.2024.1640
Tartof 2024c	Tartof S.Y., Slezak J.M., et al. Effectiveness of BNT162b2 XBB vaccine against XBB and JN.1 sublineages. Open Forum Infectious Diseases, 2024;11(7):932-940. https://doi.org/10.1001/jamainternmed.2024.1640 All Tartof studies examined patients over the same data period.
Van Werkhoven 2024	van Werkhoven C.H., Valk A.W., et al. Early COVID-19 vaccine effectiveness of XBB.1.5 vaccine against hospitalisation and admission to intensive care, the Netherlands, 9 October to 5 December 2023. Euro Surveillance (European communicable disease bulletin). 2024;29(1):2300703 https://doi.org/10.2807/1560-7917.es.2024.29.1.2300703

Source: Table 2.2.2 (pp 59-63) of the submission

* The submission provided a preprint of the publication. The citation was updated during the evaluation to reflect the published version.

6.8 The key features of each of these studies as presented in the submission are summarised in Table 6. Studies are grouped by design and main intervention.

6.9 None of the studies presented was a randomised, controlled trial. Observational, non-randomised studies are inherently subject to potential bias. At the time of TGA registration, efficacy was inferred using immunobridging studies that compared the immune response elicited by raxtozinameran to that of the original BNT162b2 vaccine, based on an implicit assumption that immune response is a valid surrogate for efficacy. The ESC noted that, given the clinical urgency for updated COVID-19 vaccines as new variants circulate, immunobridging studies have been used globally (including by ATAGI) in conjunction with local epidemiology data to make recommendations regarding the use of COVID-19 vaccines. The assumption that immune response is a valid surrogate for efficacy was not assessed in the submission however the ESC considered that, in the proposed context of an ongoing vaccination program for COVID-19, it was likely to be a reasonable assumption, although it would increase uncertainty in relation to the estimated benefits of vaccination in the economic model.

Table 6: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Raxtozinameran-specific studies – non comparative						
C4591054 Substudy A	417 (412 treated)	Prospective NC ^b , OL 6 months	High	≥ 12 years, received ≥ 3 prior doses of mRNA vaccine, with most recent being BA.4/BA.5-adapted bivalent vaccine	Cases of COVID-19 or MIS-C, immunogenicity (neutralising titres, sero-response) safety	No
C4591054 Substudy B	311	Prospective NC ^b , OL 6 months	High	≥ 12 years, previously exposed to SARS-CoV-2 and were COVID-19 vaccine-naïve	Cases of COVID-19 or MIS-C, immunogenicity (neutralising titres, sero-response) safety	No

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Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Raxtozinameran-specific studies – cohort studies						
Hansen 2024	1,037,479 people	Retrospective population-based cohort analysis 3 weeks (8 Oct to 26 Oct 2023) Denmark	High	≥ 65 years, previously vaccinated	VE for COVID-19-related hospitalisations	Yes
Huiberts 2024	23,895	Prospective cohort study 3 months 9 Oct 2023 to 9 Jan 2023 Netherlands	High	≥ 18 in a medical risk group or healthcare workers and ≥ 60 years	VE for self-reported SARS-CoV-2 infection	No
Monge 2024	65-79 years: 1.9 million person-days ≥ 80 years: 1 million person-days	Cohort study 2 months (Oct to Nov 2023) 7 countries in the VEBIS network, Europe	High	≥65 years, previously immunised	VE for COVID-19 hospitalisation and death	Yes
Nunes 2024	20,183,622	Historical cohort ~ 6 weeks (Dec 2023 to Feb 2024) 7 countries in the VEBIS network, Europe	High	≥ 65 years, community dwelling, previously vaccinated	VE for COVID-19-related hospitalisations & deaths	Yes
Raxtozinameran-specific studies – case-control studies						
Antunes 2024	622 cases 3,457 controls	MC, test-negative case-control 3 months (5 Oct 2023 to 14 Jan 2024) 6 countries in the VEBIS network, Europe	High	≥ 18 years hospitalised with severe acute respiratory infection	VE for SARS-CoV-2 hospitalisations	Yes
Caffrey 2024	20,523 cases 92,651 controls	MC, test-negative case-control 4 months 25 Sep 2023 – 31 Jan 2024 USA	High	≥ 18 years with acute respiratory infection episode in the US VA Healthcare System	VE for COVID-19 hospitalisation, ED/UC visits, and outpatient visits.	Yes
Delaunay 2024	1,057 cases 4,397 controls	MC, test-negative case-control 3 months (5 Oct 2023 to 14 Jan 2024) 11 countries in the VEBIS network, Europe	High	≥ 5 years with sudden onset of symptoms of acute respiratory illness	VE for medical attendance for SARS-CoV-2 infection	No

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Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Nguyen 2024	308 cases 1117 controls	MC, test-negative case-control 6 months (Oct 2023 to Apr 2024) USA id.DRIVE network including study sites in Belgium, Germany, Italy, and Spain.	High	≥18 years old, hospitalised for ≥ 1 night stay with SARI	VE for JN.1-related COVID-19 hospitalisation	Yes
Tartof 2024c	7,572 cases; 44,464 controls	MC, test-negative case-control 5 months (Oct 2023 to Feb 2024) Kaiser Permanente Southern California (KPSC) health system, USA	High	≥ 18 years old seeking testing due to ARI	VE for symptomatic COVID-19, hospitalisation, ED/UC visits	Yes
Raxtozinameran-specific studies – screening studies						
Van Werkhoven 2024	2,050 hospitalised patients	Screening method-based observational study ~ 2 months Oct 2023 – Dec 2023 Netherlands	High	≥ 60 years, previously vaccinated and hospitalised for COVID-19	VE for COVID-19 hospitalisation and ICU admission	Yes
Cohort studies of any XBB.1.5-adapted mRNA vaccine (raxtozinameran or andusomeran)						
Andersson 2024	3,898,264 (after matching)	MC, retrospective matched cohort (TTE) 24 weeks 1 Oct 2023 to 21 Apr 2024 Denmark, Finland, Sweden	High	≥ 65 years, previously vaccinated (≥ 4 doses) with no prior hospitalisation for COVID-19	VE for COVID-19-related hospital admissions & deaths	No
Lin 2024a	~2,000,000	Cohort study 6 weeks (11 Sep to 27 Nov 2023) Nebraska, USA	High	≥ 6 months	Incidence of SARS-CoV-2 infection Incidence of death	No
Lin 2024b	~1,800,000	Cohort study 5 months (11 Sep to 27 Nov 2023) Nebraska, USA	High	≥ 6 months	VE against COVID-19 infection, hospitalisations and deaths	

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Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Liu 2024	~4,120,000	Cohort study 6 months 1 Aug 2023 to 29 Feb 2024 Australia	High	≥ 65 years	VE against death	No
Case-control studies of any XBB.1.5-adapted mRNA vaccine (raxtozinameran or andusomeran)						
DeCuir 2024	VISION network: 4,589 cases 32,914 controls IVY network: 1,194 cases 2923 controls	MC, test-negative case-control 4.5 months (21 Sep 2023 to 31 Jan 2024) USA	High	≥ 18 years, immunocompetent, hospitalised for a COVID-19-like illness	VE for COVID-19-related ED/UC visits, VE for COVID-19-related hospitalisations	No
Link-Gelles 2024a Link-Gelles 2024b Link-Gelles 2024c	7,176 cases 63,654 controls	MC, test-negative case-control 7 months (Sep 2023 to Apr 2024) USA	High	≥ 6 months	VE against symptomatic SARS-CoV-2, COVID-19-ED/UC encounters, COVID-19-associated hospitalisations, by immunocompromise status, COVID-19-associated critical outcomes	Yes
Nham 2024	461 cases 461 controls	MC, test-negative matched (on age group and sex) case-control study 1 month (Nov 2023) Korea	High	≥ 19 years undergoing testing for COVID-19 at participating hospitals	VE for symptomatic COVID-19	No
Shrestha 2024a Shrestha 2024b	48,210 47,561 (subanalysis)	Retrospective cohort study ~ 6 months Oct 2023 to Apr 2024 Ohio, USA	High	Healthcare workers (employees of Cleveland Clinic)	VE for COVID-19	No
Other studies of any XBB.1.5-adapted mRNA vaccine (raxtozinameran or andusomeran)						
Moustsen-Helms 2024	3,862 SARS-CoV-2 positive cases	Observational study 6 months (Sep 2023 to Feb 2024) Denmark	High	≥18 years with confirmed SARS-CoV-2 infection	Relative vaccine protection against different SARS-CoV-2 variants.	No

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Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Studies of any COVID-19 booster (including original monovalent, bivalent booster or XBB.1.5-adapted mRNA vaccines; not restricted to raxtozinameran)						
Chong 2024	3,086,562 in the total group. Of these, 3.2% (107,966) were vaccinated with XBB.1.5-adapted vaccines	Population-based cohort analysis 7 weeks 26 Nov 2023 to 13 Jan 2024) Singapore	High	≥ 18 years who had received ≥ 3 mRNA vaccines; updated formulations were recommended for all adults aged ≥ 60 years & strongly encouraged for all adults aged ≥ 18; to be included in the study, boosters were to be administered 1 year (and no less than 5 months) after the last dose	Incidence of SARS-CoV-2 infection, COVID-19-associated ED visits, COVID-19-associated hospitalisations	No
Kirsebom 2024	4,351 cases 10,227 controls	MC, test-negative case-control 3 months (4 Sep 2023 to 21 Jan 2024 England	High	≥ 18 years, immunocompetent, hospitalised for an acute respiratory illness	VE for COVID-19-related hospitalisations	No
Other studies - bretovameran						
Diya 2024 C4591054 – JN.1	53	NC ^a , OL 6 months	High	≥ 18 years	Immunogenicity (neutralising titres, sero-response) safety	No

Source: Table 2.2.1 (pp55-58 of the submission), BNT162b2 study C4591054 Sections 2.3.3, 2.4.3 (pp66-67, 72-74 of the submission), Studies with Omicron XBB.1.5 vaccines for recent variants Sections 2.3 & 2.4 (pp126-135 of the submission), Substudy of BNT162B2 study C4591054 – BNT162B2 JN.1 vaccine Sections 2.3.1 – 2.4 (pp117-119 of the submission)

ARI = acute respiratory illness; ED/UC = emergency department/urgent care; MC = multi-centre; MIS-C = multisystem inflammatory syndrome in children; NC = non-comparative; OL = open label; SARI = severe acute respiratory infection; TTE = target trial emulation; USA = United States of America; VA= Veterans Affairs; VE = vaccine efficacy; VEBIS = Vaccine Effectiveness, Burden and Impact Studies

^b The submission describes the study as a randomised controlled trial however the study involved the administration of raxtozinameran in all subjects. There were two arms in the study but these were predicated on age of the subjects (12 -55 years or > 55 years)

Comparative effectiveness

6.10 Although the submission presented a full reporting of outcomes from each of the reports listed in Table 6, the evaluation focussed on results of studies that presented an estimate of vaccine efficacy (VE) for boosters with a monovalent XBB.1.5-adapted vaccine in terms of hospitalisations, intensive care admissions or death, consistent with the ATAGI pre-submission advice to PBAC (29 August 2024).

6.11 The key results from each of the studies with analyses reporting VE for hospitalisation and presented in the submission, are summarised in Table 7. The studies presented are grouped by intervention and by design (i.e., cohort, case-control or other). Five studies reported VE for deaths and these results are also included in Table 7. The results suggest that VE for death is no worse than VE for hospitalisation.

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- 6.12 Only two studies reported VE for intensive care admissions. Link-Gelles 2024c reports VE of 59% (95% CI: 50% to 67%) for immunocompetent adults and van Werkhoven 2024 report VE for ICU admission of 73.3% (95% CI: 42.2% to 87.6%). Although the evidence is very limited, the results suggest that VE for ICU admission is no worse than VE for hospitalisation.
- 6.13 As can be seen from Table 7, there is a wide variation in estimates of VE for hospitalisations. There are many factors that may be contributing to the variations in estimates of VE. For example, the studies are heterogeneous in terms of study design, populations recruited, duration of follow-up, vaccine intervention (i.e., raxtozinameran or XBB.1.5-adapted mRNA vaccines generally), and the timing of the study relative to predominant circulating sub-variants of SARS-CoV-2.
- 6.14 The evaluation noted there is likely to be some overlap in the populations included in some of the studies in terms of geography, time period, and study networks. To give a specific example of overlap, the analyses reported by Andersson 2024 and the analyses reported by Hansen 2024, both included people aged ≥ 65 years in the Danish national registry with data available from 8 to 26 October 2023. Similarly, the analyses by De Cuir 2024 and by Link-Gelles 2024 were both based on data from the VISION hospital network in the USA.
- 6.15 It is also important to note that none of the studies report VE over a period longer than 7 months and many reported VE over 3 months or less.

Table 7: Vaccine efficacy for hospitalisation and death for total populations included in the studies presented in the submission

Trial	N	Design/ duration/region	Predominant variants	Patient population	VE% hospitalisation (95% CI)	VE% deaths (95% CI)
Raxtozinameran-specific studies						
Caffrey 2024	20,523 cases 92,651 controls	Test-negative case-control 4 months 25 Sep 2023 – 31 Jan 2024 USA	XBB lineages initially then JN.1 was predominant from mid-late Dec 2023	≥ 18 years with acute respiratory infection episode in the US VA Healthcare System	43 (34 to 51)	NR
Nguyen 2024*	308 cases 1117 controls	MC, test- negative case- control 6 months (Oct 2023 to Apr 2024) USA id.DRIVE network including study sites in Belgium, Germany, Italy, and Spain.	JN.1	≥ 18 years old, hospitalised for ≥ 1 night stay with SARI	53.8 ^a (38.4 to 65.4) with no evidence of waning up to 5 months post- vaccination	NR

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Trial	N	Design/ duration/region	Predominant variants	Patient population	VE% hospitalisation (95% CI)	VE% deaths (95% CI)
Nunes 2024*	20,183,622	Historical cohort ~ 2-3 months (Dec 2023 to Feb 2024) 7 countries in the VEBIS network, Europe	BA.2.86 and JN.1	≥65 years, community dwelling, previously vaccinated	65-79 years: 50.2 ^a (44.6 to 55.2) ≥ 80 years: 40.7 ^a (35.1 to 45.9)	65-79 years: 57.5 ^a (41.5 to 69.1) ≥ 80 years: 48.4 ^a (38.2 to 56.9)
Tartof 2024c	7,572 cases; 44,464 controls	MC, test- negative case- control 5 months (Oct 2023 to Feb 2024) Kaiser Permanente Southern California (KPSC) health system, USA	XBB.1.5 was dominant initially then JN.1 became the most prevalent variant in Dec 2023	≥18 years old seeking testing due to ARI	57 (45 to 66)	NR
Van Werkhoven 2024	2,050 hospitalised patients	Screening method-based observational study ~ 2 months Oct 2023 – Dec 2023 Netherlands	Not specified but timing suggests XBB.1.5-related sub-lineages were dominant with early JN.1 emergence possible	≥ 60 years, previously vaccinated and hospitalised for COVID-19	70.7 (66.6, 74.3)	NR
Cohort studies - any XBB.1.5-adapted mRNA vaccine (raxtozinameran or andusomeran)						
Andersson 2024*	3,898,264 (after matching)	Matched cohort (TTE) 24 weeks 1 Oct 2023 to 21 Apr 2024 Denmark, Finland, Sweden	XBB lineages dominated to Nov 2023 & then the BA.2.86 (including JN.1) was predominant for the rest of the study period	≥ 65 years, previously vaccinated (≥ 4 doses) & no prior hospitalisation for COVID-19	57.9 ^a (49.9 to 65.8)	75.2 ^a (70.6 to 79.9)
Hansen 2024	1,037,479 people	Population- based cohort analysis 3 weeks (8 Oct to 26 Oct 2023) Denmark	XBB.1.5	≥ 65 years, previously vaccinated	76.1 ^b (62.3 to 84.8)	NR

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Trial	N	Design/ duration/region	Predominant variants	Patient population	VE% hospitalisation (95% CI)	VE% deaths (95% CI)
Lin 2024b	~1,800,000	Cohort study 5 months (11 Sep to 27 Nov 2023) Nebraska, USA	EG.5, XBB.2.3, XBB.1.1.6 initially then HV.1 and JN.1	≥ 6 months	VE peak: 66.8 (51.7 to 77.1) at 4 weeks after vaccination, decreasing to 49.2 (7.0 to 72.2) at 14 weeks after vaccination	VE peak: 72.0 (34.0 to 88.1) at 4 weeks after vaccination, decreasing to 52.3 (11.8 to 74.2) at 14 weeks after vaccination
Liu 2024	~4,120,000	Cohort study 6 months 1 Aug 2023 to 29 Feb 2024 Australia	Initially XBB- related subvariants and then JN.1.	≥ 65 years	NR	74.7 (59.9 to 84.1)
Monge 2024	65-79 years: 1.9 million person-days ≥ 80 years: 1 million person-days	Cohort study 2 months (Oct to Nov 2023) 7 countries in the VEBIS network, Europe	High	≥65 years, previously immunised	For 65-79 year olds: 66.8 (58.1 to 73.7) For ≥ 80 years 65.9 (56.9 to 73.1)	For 65-79 year olds: 66.9 (42.2 to 81.0) For ≥ 80 years 72.3 (50.5 to 84.5)
Case-control studies - any XBB.1.5-adapted mRNA vaccine (raxtozinameran or andusomeran)						
Antunes 2024	622 cases 3,457 controls	Test-negative case-control 3 months (5 Oct 2023 to 14 Jan 2024 6 countries in the VEBIS network, Europe	XBB lineages dominated until 18 Dec 2023, when the BA.2.86 (including JN.1) variant became predominant	≥ 18 years hospitalised with severe acute respiratory infection	49 (37 to 58)	NR
DeCuir 2024	VISION hospital network: 4,589 cases 32,914 controls IVY inpatient network: 1,194 cases 2923 controls	Test-negative case-control 4.5 months (21 Sep 2023 to 31 Jan 2024) USA	XBB lineages dominated initially but the JN.1 variant became predominant in the period between 23 Dec 2023 and 6 Jan 2024	≥ 18 years, immunocompetent, previously vaccinated, hospitalised for a COVID-19-like illness	VISION network: 52 (47 to 57) IVY network 43 (27 to 56)	NR

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Trial	N	Design/ duration/region	Predominant variants	Patient population	VE% hospitalisation (95% CI)	VE% deaths (95% CI)
Link-Gelles 2024c	7,176 cases 63,654 controls	Test-negative case-control 7 months (Sep 2023 to Apr 2024 USA	XBB lineages dominated initially but the JN.1 variant became predominant in the period between 23 Dec 2023 and 6 Jan 2024	≥ 18 years, hospitalised for a COVID-19-like illness	VISION network ^c : 42 (37 to 46) VISION network immunocompromised: 29 (18 to 38) Immunocompetent in IVY network: 37 (24 to 47) Immunocompromised in IVY network: 13 (-13 to 33)	NR
Kirsebom 2024	4,351 cases 10,227 controls	Test-negative case-control 3 months (4 Sep 2023 to 21 Jan 2024 England	XBB lineages dominated initially but the JN.1 variant became predominant in December 2023	≥ 65 years hospitalised for an acute respiratory illness	VE peak for XBB.1.5- adapted vaccines: 54.8 (46.8–61.6) 2–4 weeks after vaccination VE for XBB.1.5- adapted vaccines at 10-14 weeks: 42.2 (32.3 to 50.6)	NR
Cohort studies of COVID-19 boosters (not restricted to XBB.1.5-adapted mRNA vaccines)						
Chong 2024	3,086,562 in the total group but only 3.2% of these (107,966) were vaccinated with a XBB.1.5- adapted vaccine	Population- based cohort analysis 7 weeks 26 Nov 2023 to 13 Jan 2024) Singapore	JN.1	≥ 18 years who had received ≥ 3 mRNA vaccines; updated formulations were recommended for all adults aged ≥ 60 years & strongly encouraged for all adults aged ≥ 18; to be included in the study, boosters were to be administered 1 year (and no less than 5 months) after the last dose.	42 ^b (9 to 63) for XBB.1.5-adapted mRNA vaccine, 8-120 days since last dose	NR

Source: Table 2.2.1 (pp55-58 of the submission), Studies with Omicron XBB.1.5 vaccines for recent variants Sections 2.3 & 2.4 (pp126-135 of the submission), Section 2.5 (pp167-296 of the submission)

esp = especially; MC = multi-centre

TTE = target trial emulation; VE = vaccine efficacy; VEBIS = Vaccine Effectiveness, Burden and Impact Studies

* Additional published report located during the evaluation

^a Updated results are reported in the final publication located during the evaluation

^b Estimated using the formula $VE = (1 - aHR) * 100\%$ (where aHR is the adjusted hazard ratio)

^c This is an update of results of analysis reported by De Cuir 2024

6.16 The submission stated that it limited consideration of evidence to results from 12 studies on the grounds that the use of raxtozinameran in these studies was ≥ 89%.

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Although the submission stated that 12 studies were used to inform estimates of effectiveness in the subgroups for whom NIP-listing of raxtozinameran is proposed, only 10 reports of studies were used (though some studies reported data for multiple subgroups). Of the 10 reports, 3 (Monge 2024, Nunes 2024 and Antunes 2024) used data from the VEBIS network in Europe such that there is potential for overlapping patient populations. Similarly, Tartof 2024a (published as Tartof 2024c) is an update on Tartof 2024b.

- 6.17 Using these reports, the submission provided an analysis of outcomes by age group. On the basis of the results of these analyses, the submission assumed that age was not a modifier of VE of raxtozinameran. More accurately, there is insufficient evidence to reject a null hypothesis that VE is similar in all age groups. However, the limitations of the available evidence make this conclusion uncertain, including the potential for bias due to the observational design of the studies, the paucity of reporting of results by age group, and the absence of formal tests for treatment effect modification.
- 6.18 The submission provided an analysis intended to estimate VE for immunocompetent vs immunocompromised people. Results for the three studies that reported results by immune status are summarised in Table 8. The submission stated that: “it is widely assumed that an immunocompromised status is likely to yield a lower VE”. No further information was presented regarding immune status as a potential modifier of VE. Although results from two of the three studies suggest a trend toward reduced VE of raxtozinameran in immunocompromised people, it is uncertain whether there is sufficient evidence to reject a null hypothesis that VE is similar regardless of immune status. It is, however, biologically plausible that patients with compromised immune systems may not respond to vaccines in the same way as immunocompetent people. This is discussed further in paragraph 6.28 and 6.29.

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Table 8: Vaccine efficacy for hospitalisation by immune status

Study	Design/duration/ region	N	Overall VE (95% CI)	VE (95% CI) Immunocompetent	VE (95% CI) Immunocompromised
Nguyen 2024*	Test-negative case-control 6 months (Oct 2023 to Apr 2024) USA id.DRIVE network including study sites in Belgium, Germany, Italy, and Spain.	308 cases 1117 controls	53.8 ^a (38.4 to 65.4)	NR	56.0 (22.5 to 75.0)
Caffrey 2024	Test-negative case-control 4 months Sep 2023 – Jan 2024 USA	20,523 cases 92,651 controls	43 (34 to 51)	49 (38 to 58)	33 (16 to 47)
Link-Gelles 2024c	Test-negative case-control 7 months (Sep 2023 to Apr 2024) USA	7,176 cases 63,654 controls	Only reported by immune status	VISION network: 42 (37 to 46) IVY network: 37 (24 to 47)	VISION network: 29 (18 to 38) IVY network: 13 (-13 to 33)

Source: Table 2.6.2 (p299 of the submission) and the published reports of the studies

CI = confidence interval; VE = vaccine efficacy

* Additional published report located during the evaluation

^a Updated results are reported in the final publication located during the evaluation

6.19 The submission provided an analysis intended to inform how the change in the predominant SARS-CoV-2 variant affected VE of raxtozinameran. VE by period of predominant SARS-CoV-2 variant in circulation is summarised in Table 9. As noted in the submission, there was a clear trend suggesting reduced VE of raxtozinameran against the JN.1 variant in studies that reported VE by time period.

Table 9: Vaccine efficacy for hospitalisation by predominant SARS-CoV-2 variant in circulation

Study	Design/duration/ region	N	Overall VE (95% CI)	VE (95% CI) during period when XBB.1.5 was predominant (to mid-Dec 2023)	VE (95% CI) during period when JN.1 was predominant (from late Dec 2023)
Hansen 2024	Population-based cohort analysis 3 weeks (8 Oct to 26 Oct 2023) Denmark	1,037,479 people (442,247 vaccinated, 867,645 unvaccinated)	76.1 ^b (62.3 to 84.8)	76.1% (62.3–84.8) in first 2–3 weeks after XBB.1.5 booster (short-term)	N/A (study period precedes JN.1 wave)

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Study	Design/duration/ region	N	Overall VE (95% CI)	VE (95% CI) during period when XBB.1.5 was predominant (to mid-Dec 2023)	VE (95% CI) during period when JN.1 was predominant (from late Dec 2023)
Monge 2024	Cohort study 2 months (Oct to Nov 2023) 7 countries in the VEBIS network, Europe	65-79 years: 1.9 million person-days ≥ 80 years: 1 million person-days	Only reported by age subgroups	For 65–79-year-olds: 66.8 (58.1 to 73.7) For ≥ 80 years 65.9 (56.9 to 73.1)	N/A (study period precedes JN.1 wave)
Nunes 2024*	Cohort ~ 2-3 months (Dec 2023 to Feb 2024) 7 countries in the VEBIS network, Europe	20,183,622 people	Only reported by age subgroups	N/A (study initiated when ≥ 80% of SARS-CoV-2 were BA.2.86/JN.1).	65-79 years: 50.2 ^a (44.6 to 55.2) ≥ 80 years: 40.7 ^a (35.1 to 45.9)
Antunes 2024	Test-negative case- control 3 months (5 Oct 2023 to 14 Jan 2024) 6 countries in the VEBIS network, Europe	622 cases 3,457 controls	49 (37 to 58)	NR separately though the study period spanned XBB to BA.2.86/JN.1 transition	
Nguyen 2024*	Test-negative case- control 6 months (Oct 2023 to Apr 2024) USA id.DRIVE network including study sites in Belgium, Germany, Italy, and Spain.	308 cases 1117 controls	53.8 ^a (38.4 to 65.4)	N/A (focused on JN.1 period only).	53.8 ^a (38.4 to 65.4)
Caffrey 2024	Test-negative case- control 4 months Sep 2023 – Jan 2024 USA	20,523 cases 92,651 controls	43 (34 to 51)	62 (44 to 74)	32 (3 to 52)
Tartof 2024b	Test-negative case- control 5 months (Oct 2023 to Dec 2023) Kaiser Permanente Southern California health system, USA	2,854 cases 15,345 controls	62 (32 to 79)	62 (32 to 79)	N/A (JN.1 was not predominant)
Tartof 2024c	Test-negative case- control 5 months	7,572 cases; 44,464 controls	57 (45 to 66)	65 (41 to 79)	54 (33 to 69)

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Study	Design/duration/ region	N	Overall VE (95% CI)	VE (95% CI) during period when XBB.1.5 was predominant (to mid-Dec 2023)	VE (95% CI) during period when JN.1 was predominant (from late Dec 2023)
	(Oct 2023 to Feb 2024) Kaiser Permanente Southern California health system, USA				
Van Werkhoven 2024	Screening method-based observational study ~ 2 months Oct 2023 – Dec 2023 Netherlands	2,050 hospitalised patients	70.7 (66.6, 74.3)	70.7 (66.6, 74.3)	N/A (study ended before JN.1 became predominant).
Link-Gelles 2024c	Test-negative case-control 7 months (Sep 2023 to Apr 2024 USA	7,176 cases 63,654 controls	Only reported by immune status	54 (36 to 67)	33 (2 to 54)

6.20 The submission attempted to pool results from various analyses such as those shown in Table 8 and Table 9 to provide summary estimates of VE in different populations under different conditions. The results of the submission's synthesis of evidence are shown in Table 10. The evaluation noted the following issues with the submission's approach to synthesis of the data to derive weighted average estimates:

- The pooling of studies used a weighted average approach that assumed the weighting of populations within each of the studies reflected the weighting that would apply in clinical practice. Given the differences in the eligibility criteria applied in the studies, this assumption may not be valid.
- There is likely to be some overlap in the populations included in some of the studies in terms of geography, time period, and study networks. To give a specific example of overlap, the analyses reported by Andersson 2024 and the analyses reported by Hansen 2024, both included people aged ≥ 65 years in the Danish national registry with data available from 8 to 26 October 2023. Similarly, the analyses by De Cuir 2024 and by Link-Gelles 2024 were both based on data from the VISION hospital network in the USA.
- The pooling of data from Monge 2024 and Antunes 2024 was inappropriate given that there was overlap in the study populations (both included data from October – November 2023 from the VEBIS network).
- An identical population size (N=113,174) was applied from Caffrey 2024 during both the XBB.1.5 and JN.1 time periods, derived from the total study population included in the overall analyses. The evaluation considered this was incorrect, because the reported data referred to two separate subgroups of patients as indicated in Figure 2 of the paper. Thus, results from Caffrey may be overweighted

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in the analyses, but the individual subgroup sizes were not available to inform more appropriate weighting.

- Identification of new publications might alter the weighted average VE, noting the literature search for the submission was conducted in August 2024.

6.21 The evaluation noted that none of the studies report VE over a period longer than 7 months and many reported VE over 3 months or less.

Table 10: Vaccine efficacy for hospitalisation by predominant SARS-CoV-2 variant in circulation

Time period month 1 to 3 (XBB.1.5 predominant)				Time period month 4 to 6 (JN.1 predominant)			
Study (age)	Population size	Vaccine efficacy	Variant	Study (age)	Population size	Vaccine efficacy	Variant
Immunocompetent population (standard and high risk)							
Hansen 2024 (65+)	1,037,479	76.1%	XBB				
Monge 2024 (65-79)	3,092,798	66.8%	XBB	Nunes 2024 (65-79)	4,560,138	47.3%	JN.1
Monge 2024 (80+)	1,401,212	65.9%	XBB	Nunes 2024 (80+)	1,973,586	35.9%	JN.1
Antunes 2024b (18+)	1,684	49%	XBB				
Caffrey 2024 (18+)	113,174	62%	XBB	Caffrey (18+)	113,174	37%	JN.1
Tartof 2024a (18+)	52,036	74%	XBB	Tartof 2024a (18+)	52,036	54%	XBB&JN.1
				Nguyen 2024 (18+)	834	56.7%	JN.1
				Nguyen 2024 (18+)	740	59.9%	JN.1
Total population size	5,698,383			Total population size	6,700,508		
Weighted average		68.24%				43.82%	
Immunocompromised population							
Nguyen 2024 (18+)	288	56%	JN.1				
Caffrey 2024 (18+)	40,309	33%	XBB				
Link-Gelles 2024c (18+)	1,515	38%	XBB&JN.1	Link-Gelles 2024c (18+)	1,677	27%	XBB&JN.1
Link-Gelles 2024c (18+)	1,677	27%	XBB&JN.1	Link-Gelles 2024c (18+)	1,080	7%	XBB&JN.1
Total population size	43,789			Total population size	2,757		
Weighted average		33.09%				19.17%	

VE over 6 months

6.22 The submission used the weighted averages calculated in Table 10 to derive estimates of VE of raxtozinameran for hospitalisation over 6 months. To derive the estimate of average VE over 6 months (presented in Table 11), the submission weighted the average VE over 3 months while the XBB.1.5 variant was predominant with the VE from 4-7 months while the JN.1 variant was predominant, by the total population sizes from which those estimates were derived (e.g., for the immunocompromised group it calculated an average VE for raxtozinameran over 6 months of 32.27% $(43,789/(43,789+2,757) \times 33.09\%) + (2,757/(43,789+2,757) \times 19.17\%)$). The ESC concluded that this was not appropriate. For both the immunocompetent and the immunocompromised groups, the weighting should be determined by time (i.e., 50/50 for months 1 to 3 and for months 4 to 6) to report the average VE over the period during which the studies were conducted.

6.23 The evaluation noted, that beyond the concern about the calculations performed, it was important to consider which estimates of VE will be most relevant for decision-making, i.e. whether it is reasonable to propose a weighted average VE of

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raxtozinameran based on earlier time periods in which XBB.1.5 was predominant or whether VE of raxtozinameran now and into the future is most relevant. In regard to future VE, the evolution of SARS-CoV-2 can be rapid and remains unpredictable (as discussed in paragraph 4.8). Further, as noted by the submission, vaccines that are better matched to currently circulating variants offer enhanced protection compared with vaccines adapted to respond to previous variants (paragraph 4.12). In summary, the future VE of raxtozinameran (or any COVID-19 vaccine) is difficult to estimate, given the expectation of future changes in circulating variants. It is anticipated that further adapted vaccines will be developed to address new variants, such as bretovameran matched to the JN.1 SARS-CoV-2 variant 1. However, it remains uncertain if these vaccines will have a similar VE to raxtozinameran if they are proposed for NIP listing in the future. The ESC noted that another uncertainty relevant to estimation of VE is natural immunity arising from past infection in the population, and that the term "hybrid immunity", is used to reflect protection from both vaccination and infection.

VE from 7 to 12 months

- 6.24 In addition to estimating VE over 6 months, the submission attempted to estimate VE beyond the time horizon for which data of VE were available (i.e., from 7 to 12 months) (see Table 10). The submission assumed a linear decline in VE during the period from 7 to 12 months. VE at the start of this period was assumed to be equivalent to the average VE observed in months 4-6 following administration of the vaccine as estimated in Table 10 and VE at the end of the 7-12 month period was estimated by assuming there would be residual VE at 12 months after vaccination of 17.3% for the immunocompetent population (at standard or high risk of severe COVID-19). This estimate was based on the midpoint of a residual VE of 11% (for those had previously received a BA.4/5 bivalent vaccine but no XBB vaccine) to 25% (for those ≥ 3 doses of original wild-type vaccine but no variant-adapted vaccines of any kind), as reported in Table 3 of the supplement to Tartof 2024b. According to that table, residual VE against hospitalisation was not statistically significantly different to zero (95% CIs were -32% to 39% around the 11% point estimate and -17% to 52% around the 25% estimate, respectively). The ESC considered the application of a residual VE was therefore not adequately justified by the available evidence. A more appropriate assumption would have been to assume no residual VE by 12 months (or sooner). The submission also assumed a residual VE of 3.31% at 12 months after vaccination in the immunocompromised group, which assumed that 10% of the initial VE for the immunocompromised group (33.09%) would remain. The application of residual VE in this population was not adequately justified.
- 6.25 Based on this approach, the submission estimated average VE over 12 months as summarised in Table 11. The evaluation concluded that overall, the approach to estimation of VE over 12 months for raxtozinameran for hospitalisation included some assumptions that were not adequately supported (e.g., assumptions of ongoing benefit beyond the time horizon examined by the studies, the application of

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inappropriate weighting of various studies, assumption that evidence from a time when XBB.1.5 was circulating remains applicable). Furthermore, the submission did not present the extent of uncertainty around the estimates calculated in Table 11. The ESC considered the approach to estimation of VE to apply over 12 months to be inappropriate, particularly the approach to pooling of results from different time periods. The ESC advised that the approach to combining data across various time ranges was inappropriate. The ESC considered duration of VE to be uncertain and potentially overestimated. It also advised that it would have been appropriate for a confidence interval around vaccine efficacy to have been estimated using traditional meta-analytic techniques. It noted that uncertainty and reporting biases due to the observational nature of the studies would apply beyond such calculated confidence intervals.

- 6.26 Regarding the estimation of VE for people who are immunocompetent vs those who are immunocompromised, the ESC noted that the results of this analysis were associated with a high degree of uncertainty and noted that, although VE was potentially reduced in people who are immunocompromised, their background risk of severe disease was higher and there was thus greater clinical need for vaccination of these populations.
- 6.27 The ESC advised that the approach to estimation of VE over 12 months of raxtozinameran for hospitalisation included some assumptions that potentially biased estimates in favour of raxtozinameran (e.g., assumptions of ongoing benefit beyond the time horizon examined by the studies, inappropriate weighting of various studies. The ESC noted the submission’s assertion that the presented evidence for raxtozinameran was applicable for estimating VE for the proposed circumstances of use, noting it was derived from a time when XBB.1.5 was circulating, however considered the estimates of VE were likely overestimated by the submission as it had not factored in waning VE that would occur when there was a change in circulating variants prior to introduction of a future adapted vaccine. The pre-PBAC response argued that the submission had considered waning due to changes in circulating variants because of the submission’s method utilised VE for raxtozinameran from two time periods (month 1 to 3 from when XBB.1.5 predominant and month 4 to 6 when JN.1 was predominant).

Table 11: Summary of average VE of raxtozinameran for hospitalisation over 6 and 12 months as calculated by the submission

VE month 1-3	VE month 4-6	VE assumed over months 1-6	VE at start on month 7	Residual VE at 12 months	Average VE over months 7-12	Average VE over 12 months
Immunocompetent population (standard or high-risk patients)						
68.24%	43.82%	55.04%	43.82%	17.33%	30.58%	42.81%
Immunocompromised population						
33.09%	19.17%	32.27%	19.17%	3.31%	11.24%	21.75%

- 6.28 Estimates presented in Table 11 were applied in the first year of the modelled economic analysis, as summarised in Table 12. As detailed in Table 4, there were

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inconsistencies across the submission in the assumed number of doses administered in different patient subgroups. The submission’s economic analysis assumed maximum use of raxtozinameran in those receiving boosters and thus applied the maximum estimated VE that was applicable. The assumption that immunocompromised patients aged ≥ 75 years would have VE over 12 months of 55.04% (as assumed in the submission’s economic model) was not appropriate given the submission’s contention that VE in immunocompromised patients is less than in immunocompetent patients. The PSCR provided updated VE for the age 75+ All-Risk group, this resulted in a reduction of VE from 55.04% to 53.31%.

- 6.29 As described above, the submission provided an analysis intended to estimate VE for immunocompetent vs immunocompromised people in which two of the three included studies suggested a trend toward reduced VE of raxtozinameran in immunocompromised people. No further information was presented regarding immune status as a potential modifier of VE (see paragraph 6.18).

Table 12: Vaccine efficacy applied in the economic analysis (submission base case)

Age group	Risk category	Assumed doses per year in the economic evaluation (PSCR if different)	Proportion receiving dose (PSCR if different)	Proportion receiving dose corrected during evaluation ^c	VE over 12 months against hospitalisation (PSCR if different)
18 – 64 years	Standard	1	0.07% ^a	2.03%	42.81%
	High	1	50%	n/a	42.81%
	IC	2 (1)	90% (100%)	n/a	32.27% (21.75%)
64 – 75 years	Standard	1	18.87%	21.69%	42.81%
	High	2 (1)	80%	n/a	55.04% (42.81%)
	IC ^a	2	90% (100%)	n/a	32.27%
≥ 75 years	Standard	2	28.62%	31.60%	55.04%
	High	2	80%	n/a	55.04%
	IC	2	100%	n/a	32.27% ^b
	AR	2	49.36%	n/a	53.31%

a. Submission incorrectly applied 0.7%, this was corrected in the model provided with PSCR to 0.07%.

b. Submission incorrectly applied 55.04%, this was corrected in the model provided with PSCR to 32.27%.

c. Financial estimates corrected during evaluation to remove double-counting, see Table 24.

Source: Economic analysis provided with the submission.

Comparative harms

- 6.30 None of the observational studies providing evidence of vaccine efficacy in the submission specifically reported safety outcomes.
- 6.31 The submission reported that, based on non-comparative safety data from Substudy A and Substudy B of Study C4591054, the reactogenicity and AE profile of raxtozinameran were generally similar to those reported for the original BNT162b2 and BNT162b2 bivalent (WT/OMI BA.4/BA.5) vaccines. The submission did not provide

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an overview of safety outcomes that have been reported for the other versions of the BNT162b2 vaccine.

- 6.32 A review of data from the pivotal phase 3 trial^{16,17} and some reports of real-world studies with BNT162b2 vaccines^{18,19,20,21,22} informed the range of incidence of common AEs as presented in Table 13. Most AEs that have been reported with BNT162b2 vaccines have been mild to moderate, occur within 48 hours of vaccination and resolve within a few days.

Table 13: Range of incidence of common AEs reported for BNT162b2 vaccines

Adverse Event (AE)	Incidence (Dose 1 & 2)
Injection site pain, redness, swelling	70–85%
Fatigue	30–60%
Headache	25–50%
Chills/Fever	10–25%
Muscle aches (Myalgia)	20–40%
Joint pain (Arthralgia)	10–30%
Nausea	5–15%
Swollen lymph nodes	<5%

Source: Studies listed in paragraph 6.32.

- 6.33 The submission provided an overview of five studies examining the long-term safety of BNT162b2 vaccines (Doskaliuk 2023, Flacco 2023, Heshin-Bekenstein 2023, Paczkowska 2022 and Sriwastava 2021) and a summary of the 6th Periodic Safety Update Report (PSUR) for BNT162b2 vaccines.
- 6.34 The 6th Periodic Safety Update Report (PSUR) covering June to December 2023 detailed cumulative clinical trial exposure, based on over 69,957 participants receiving BNT162b2 vaccines in various formulations in clinical trials worldwide. By the end of

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- ¹⁶ Polack F.P., Thomas S.J., et al for the C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615. <https://doi.org/10.1056/NEJMoa2034577>
- ¹⁷ Thomas S.J., MWhatoreira E.D. Jr, et al for the C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *N Engl J Med*. 2021;385(19):1761-1773. <https://doi.org/10.1056/nejmoa2110345>
- ¹⁸ van den Ouweland F., Charpentier N. et al. Safety and reactogenicity of the BNT162b2 COVID-19 vaccine: Development, post-marketing surveillance, and real-world data. *Hum Vaccin Immunother*. 2024;31:20(1). <https://doi.org/10.1080/21645515.2024.2315659>
- ¹⁹ Shapiro Ben David, S., Baruch Gez, S., et al. Immediate side effects of Comirnaty COVID-19 vaccine: A nationwide survey of vaccinated people in Israel, December 2020 to March 2021. *Eurosurveillance*. 2022;27(13). <https://doi.org/10.2807/1560-7917.ES.2022.27.13.2100540>
- ²⁰ Tamburro M., Ripabelli G., et al. A Cross-Sectional Study of Untoward Reactions Following Homologous and Heterologous COVID-19 Booster Immunizations in Recipients Seventeen Years of Age and Older. *J Community Health*. 2022;47(5):814-821. <https://doi.org/10.1007/s10900-022-01112-5>
- ²¹ Gringeri M., Mosini G., et al. Preliminary evidence on the safety profile of BNT162b2 (Comirnaty): New insights from data analysis in EudraVigilance and adverse reaction reports from an Italian health facility. *Hum Vaccin Immunother*. 2021;17(9):2969-2971. <https://doi.org/10.1080/21645515.2021.1917236>
- ²² Lee C.W., Sa S., et al. Adverse Events and Safety Profile of the COVID-19 Vaccines in Adolescents: Safety Monitoring for Adverse Events Using Real-World Data. *Vaccines (Basel)*. 2022;10(5):744. <https://doi.org/10.3390/vaccines10050744>

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the reporting period, approximately 4.85 billion doses had been distributed worldwide, including original, bivalent, and XBB.1.5-adapted vaccines. This safety monitoring report indicated that no new safety concerns had been identified, and that key regulatory bodies such as EMA, WHO, TGA, and Health Canada continued to review reports on potential safety signals. Evaluated signals included menstrual irregularities, retinal vascular occlusion, and sensorineural hearing loss, none of which were determined to be risks associated with BNT162b2. However, postmenopausal haemorrhage and pulmonary embolism remained under investigation during the reporting period but were ultimately closed as safety concerns, in early 2024. The report also highlighted that no marketing authorisations had been withdrawn for safety reasons, and that updates to safety information included refinements to risk assessments based on accumulating data. Reported ongoing safety surveillance priorities were monitoring long-term effects, interactions with other vaccines, and use in vulnerable populations, including immunocompromised individuals and those with autoimmune diseases. Overall, the report concluded that based on real-world data and clinical trials, no significant long-term safety concerns warranting changes to regulatory guidance or risk management strategies were found.

- 6.35 The TGA has conducted safety surveillance of the BNT162b2 (Comirnaty) vaccine and reported its findings from early 2021 to late 2023²³. Overall, the TGA's findings from these surveillance activities indicated that the safety profile of the Comirnaty vaccine was consistent with clinical trial and international data, with most adverse events being mild and self-limiting.

Benefits/harms

- 6.36 There was no randomised clinical evidence to support benefits and harms statements for raxtozinameran.
- 6.37 An estimate of benefits, based on the submission's analyses is presented below, noting this is uncertain as it is derived from a model, rather than direct clinical evidence. Based on the submission's model, estimates of the number of patients hospitalised for COVID-19 in a year, the rate of uptake of booster vaccination and the effectiveness of raxtozinameran in preventing such hospitalisations, for every 10,000 people receiving a booster vaccination with raxtozinameran in comparison with no administration of a booster vaccine:
- Approximately 160 fewer people would require hospitalisation for COVID-19
- 6.38 An estimate of harms is presented below, which was sourced from the TGA-approved product information for raxtozinameran. These estimates were derived from a study of participants 18 years of age and older after receipt of booster doses (of tozinameran). Based on the reported incidence of adverse events with BNT162b2

²³ <https://www.tga.gov.au/news/covid-19-vaccine-safety-reports>

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vaccines in the product information, for every 10,000 people receiving a booster vaccine after 1.4 months follow-up, very common side effects include:

- More than 7,000 adults would experience injection site pain;
- More than 6,000 adults would experience tiredness;
- More than 4,000 adults would experience headache;
- More than 2,000 adults would experience muscle pain and chills;
- More than 1,000 adults would experience joint pain.

Additional clinical evidence

- 6.39 The submission proposed that its modelled economic evaluation assessing the incremental costs and outcomes associated with implementing a COVID-19 national immunisation program for Australian adults could be applicable to not only raxtozinameran, but also subsequent vaccines, such as bretoivameran. However, the clinical evidence base informing the estimates of VE were derived from studies of raxtozinameran (Table 10, Table 11). Other clinical evidence of the original monovalent vaccine and previous strain adaptations was included in Appendices. Appendix 1 included the first study C4591001, Appendix 2 included other RCTs, and Appendix 3 included other RWE. The PBAC noted the addendum to the pre-PBAC response which provided an overview of the BNT162b2 vaccine RCTs and real-world evidence studies, based on information provided in the submission's appendices.
- 6.40 In regard to certainty of vaccine effectiveness, the pre-PBAC response stated that after three years of successive variant-adapted formulations in use globally, including bivalent wild-type/BA.1- or wild-type/BA.4/5-adapted beginning in 2022, monovalent XBB.1.5-adapted beginning in 2023, and monovalent JN.1- or KP.2-adapted beginning in 2024, a trend has emerged showing consistency of vaccine effectiveness of BNT162b2 variant-adapted vaccines across formulations. Estimates of VE of BNT162b2 against COVID-19 hospitalisation or severe disease were reported to consistently range between 66% to 76% regardless of formulation during periods of well-matched SARS-CoV-2 variant circulation. The pre-PBAC response concluded that BNT162b2 variant-adapted formulations consistently restore protection against severe COVID-19 disease and COVID-19 hospitalisation, suggesting a high degree of certainty in the real-world evidence across three years of variant-adapted vaccine formulations. The pre-PBAC response did not address VE for periods in which there were changes in circulating variants, or for immunocompromised populations which were also relevant to the economic evaluation (Table 10).

Clinical claim

- 6.41 The submission described raxtozinameran as superior in terms of effectiveness compared with no booster vaccination and inferior in terms of safety compared with no booster vaccination.

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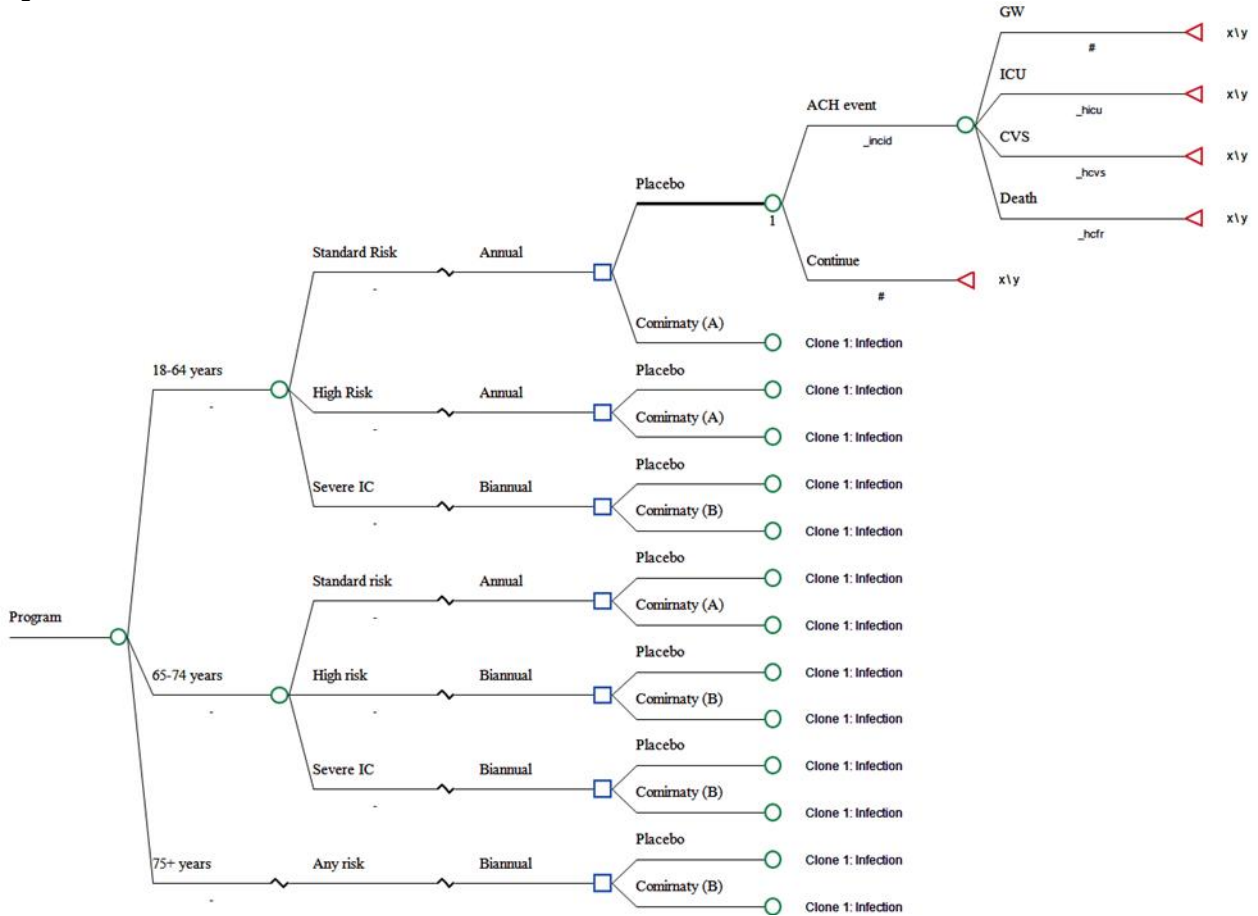
- 6.42 The ESC agreed with the evaluation that the therapeutic conclusion presented in the submission was adequately supported by the evidence presented in the submission however the magnitude of benefit and the duration of benefit was uncertain given the observational nature of the available evidence and methodological issues regarding estimation of VE in various populations.
- 6.43 The PBAC considered that the claim of superior effectiveness compared with no booster vaccination was reasonable, however the magnitude of benefit and the duration of benefit were uncertain given the observational nature of the available evidence and methodological issues regarding estimation of VE in various populations.
- 6.44 The PBAC considered that the claim of inferior safety compared with no booster vaccination was reasonable. The PBAC noted that the safety of raxtozinameran was supported by randomised clinical trials and real-world experience with earlier BNT162b2 vaccines.

Economic analysis

- 6.45 On the grounds of a claim of therapeutic superiority of raxtozinameran versus no (booster) immunisation, the submission presented a modelled cost-utility analysis comparing raxtozinameran with no immunisation.
- 6.46 The submission proposed that the modelled economic evaluation reflected the incremental costs and outcomes associated with implementing a COVID-19 national immunisation program for Australian adults using Comirnaty® (raxtozinameran or subsequent).
- 6.47 An economic analysis was performed for each of the following seven populations and a weighted incremental cost-effectiveness ratio across the total population was also presented:
- Population 1: Aged 18-64 years at standard risk of severe acute COVID-19;
 - Population 2: Aged 18-64 years at high risk of severe acute COVID-19;
 - Population 3: Aged 18-64 years with severe immunocompromise;
 - Population 4: Aged 65-74 years at standard risk of severe acute COVID-19;
 - Population 5: Aged 65-74 years at high risk of severe acute COVID-19;
 - Population 6: Aged 65-74 years with severe immunocompromise
 - Population 7: Aged 75 years or more at any risk of severe acute COVID-19.
- 6.48 The key clinical event driving the economic model was acute hospitalisation for COVID-19 with four mutually exclusive levels of severity: general ward care only, admission to an intensive care unit (ICU), continuous ventilation support (CVS) and in-hospital death. Different age groups were assigned different baseline rates of hospitalisation, ICU admission, CVS and in-hospital death based on the available AIHW

data. The same rates were appropriately applied in each treatment arm of the model. The structure of the economic model is presented in Figure 5.

Figure 5: Structure of the economic model^a



a. Figure shows booster frequency in submission base case.

Source: Figure 3.2.1 of the submission.

Abbreviations: ACH = acute COVID-19 hospitalisation; GW = general ward; ICU = intensive care unit; CVS = continuous ventilation support; A = annual vaccination; B = biannual vaccination

6.49 As shown in Figure 5, the model presented in the submission excluded consideration of any potential benefits of antiviral treatment of COVID-19. The exclusion of the potential benefits of antiviral treatments might be appropriate if the studies informing the economic evaluation permitted inclusion of subjects who received treatment with antivirals prior to hospitalisation and if antivirals were available to a similar extent as they are in the Australian setting. However, this is not the case and some of the studies informing the economic evaluation (e.g., Caffey 2024 and Tartof 2024) actively excluded patients who had received antiviral therapies. Thus, the model potentially overestimates the benefit of raxtozinameran in the proposed circumstances of use, given that antiviral treatments are available on the PBS for patients with SARS-CoV-2 infection. The PSCR argued that incorporating the benefits of antivirals in the model would be impractical due to structural complexity and uncertainty. The ESC considered that, given that the PBAC has listed the antivirals on the PBS on the basis

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that they reduce the likelihood of hospitalisation due to COVID-19, it would be appropriate for the model to reflect the reduced risk of hospitalisations due to availability of these therapies. Antivirals are a treatment option on the PBS for non-hospitalised patients who are at high risk of progression to severe COVID-19, regardless of vaccination or previous infection status. The ESC noted that sensitivity analyses around the baseline risk of hospitalisation indicated the model would be sensitive to incorporation of the effect of antivirals on baseline rates of hospitalisation. The ESC advised that it would be appropriate for the model to include estimates of the proportion of patients using antivirals in each population and apply the reduced risk of hospitalisation when antivirals are used, at rates as previously accepted by the PBAC. The pre-PBAC response argued that changes to the economic model to include antivirals were not necessary, suggesting that inclusion of additional baseline risks and antiviral costs, would likely improve cost-effectiveness for raxtozinameran compared to no booster vaccination. The response claimed that unvaccinated patients are more likely to receive an antiviral to avert progression to severe disease (hospitalisation), noting that the baseline risk of progressing to severe disease (hospitalisation) for unvaccinated patients is considerably higher than for vaccinated and/or previously infected patients.

6.50 The key components of the economic evaluation are summarised in Table 14.

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Table 14: Key components of the economic evaluation

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis	The ESC considered this was appropriate.
Perspective	Health care system	This is appropriate
Outcomes	Quality-adjusted life years gained	This is appropriate
Time horizon	One year in the model with a lifetime QALY loss payoff attributed to those who died during the one-year model period.	This is reasonable and consistent with the ATAGI advice. The ESC considered this was appropriate.
Methods used to generate results	Decision-tree analysis stratified by seven populations	This is reasonable. The model structure is approximately consistent with models previously considered by the PBAC for COVID-19 therapies ^a . The ESC considered this was generally appropriate except for the exclusion of consideration of the impact of availability of antivirals to treat COVID-19. The ESC noted that the model, reasonably, did not assume an impact on incidence of long COVID. The ESC considered this was appropriate.
Health states	Hospitalisation is classified into general ward, ICU, CVS and in-hospital death	This is reasonable and consistent with the ATAGI advice. The ESC considered this was appropriate.
Transition probabilities	Baseline mortality and morbidity event risks for the placebo group have been estimated from recent Australian epidemiological data (AIHW). VE has been estimated based on an assessment of the totality of recent real-world evidence	The ESC considered the derivation of baseline mortality and morbidity events using AIHW data to be reasonable. The extent of and duration of vaccine efficacy is the key input in the economic model driving differences in outcomes across treatment arms. The evidence for the extent of vaccine efficacy in each of the subgroups for which an economic evaluation is performed is uncertain. In addition, the duration of vaccine efficacy is uncertain.
Discounting	5% p.a. on QALYs lost due to deaths in the 1 st year of the model	This is reasonable
Software package	Microsoft Excel	This is reasonable

Source: Table 3.1.1 of the submission.

Abbreviations: ATAGI = Australian Technical Advisory Group on Immunisation; CVS = continuous ventilatory support; ICU = intensive care unit; QALY = quality-adjusted life year; VE = vaccine efficacy

^a PBAC considerations of molnupiravir, July 2023 PBAC meeting and nirmatrelvir and ritonavir, November 2023 PBAC meeting.

6.51 As detailed in Table 4, there were inconsistencies across different sections of the submission in the assumed number of doses administered in different patient subgroups. The economic analysis assumes that, when used, raxtozinameran will be used the maximum number of times recommended by ATAGI e.g., where the ATAGI recommendation for immunocompromised people aged 18-74 years is for administration of a vaccine every 12 months but advises these individuals “can consider” a dose every 6 months based on individual risk-benefit assessment, the submission’s base case assumed that all immunocompromised people aged 18-74 who elect to use raxtozinameran will be administered two doses; this impacts both costs and effectiveness assumed in the economic analysis. In summary, the economic analysis assumed maximum use of raxtozinameran in those receiving boosters and also applied the maximum estimated VE that is applicable (Table 12). Revised treatment assumptions were provided in the PSCR that were aligned with Section 4, however some of these were not consistent with ATAGI advice (see Table 4).

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- 6.52 The submission acknowledged the significant issues associated with the application of current epidemiological data and clinical evidence to the target populations and the current treatment landscape of COVID-19. These issues included:
- Currently available information relates to historical SARS-CoV-2 strains, levels of vaccine induced and/or natural immunity, testing and reporting regimens, patterns of use of antiviral medicines, public health measures, clinical management protocols, health system capability and capacity, and community perceptions and behavioural responses, that are all unlikely to persist in 2025;
 - The most recent and robust Australian epidemiological data, sourced from the AIHW admitted patient care dataset relate to a mix of adequately/recently vaccinated and unvaccinated individuals, during 2022-23;
 - The available randomised controlled trial evidence for BNT162b2 cannot provide reliable estimates of the likely effectiveness of contemporary versions of the vaccine against current or future circulating variants of the virus.
- 6.53 An error was identified in the economic model during evaluation. The calculation of the general ward event rate in the “PBO” and “COM” sheets of the economic model (row 6) omitted intensive care unit (ICU) admission when estimating the proportion of hospitalised patients treated in the general ward. The general ward membership should have been calculated as one minus the membership in the other hospitalised events (ICU admission, continuous ventilatory support [CVS] and in-hospital death) rather than one minus CVS and in-hospital death. Without correcting the error, the economic model overestimated the proportion of patients being hospitalised (i.e., the sum of general ward, ICU admission, CVS and in-hospital death membership was greater than one). Results of the economic evaluation were corrected for this error. The weighted base case ICER increased from \$0 to < \$5,000 per QALY gained to \$0 to < \$5,000 per QALY gained.
- 6.54 The key cost inputs to the model are summarised in Table 15. The ESC advised that the assumption of a \$7 administration fee on the basis that this fee was accepted for RSV vaccination was not justified. The patterns of administration of vaccines do not necessarily translate from one condition to another. The ESC noted the sensitivity of the results of the modelled economic evaluation to the administration fee and noted that the pharmacist service fee for administering NIP vaccines is \$19.32. Overall, the ESC advised that administration costs were underestimated in the economic analysis. Current reports on COVID vaccination indicate that approximately 30% of vaccinations have been conducted in pharmacy (COVID-19 vaccine rollout update – 11 April 2025²⁴).

²⁴ <https://www.health.gov.au/sites/default/files/2025-04/covid-19-vaccine-rollout-update-11-april-2025.pdf>

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Table 15: Cost inputs to the model

Description	Cost	Source	Comment
Raxtozinameran	\$█	Proposed by the submission	
Vaccine administration	\$7.00	Assumption based on 0.36 services of MBS item 3	This assumption does not appear reasonable. The submission provides limited justification for the administration fee. Pharmacists can receive a service fee of \$19.32 per vaccination ²⁵ .
Hospitalisation in a general ward	\$8,712	AR-DRG code E62A/B	This appears reasonable.
Hospitalisation with ICU admission	\$26,187	AR-DRG code E41A/B	This appears reasonable.
Hospitalisation with continuous ventilation support	\$49,213	AR-DRG code E40A/B	This appears reasonable.
Death	\$28,037	Simple average of the above hospitalisation costs	This appears reasonable. In the absence of a specific death-related cost, the submission assumed an equal proportion of patients that die have been managed across the hospitalised settings.

Source: p347 of the submission. Note: ICU cost was incorrectly presented in the submission.

Abbreviations: AR-DRG = Australian refined diagnosis-related group; ICU = intensive care unit; MBS = Medicare Benefits Schedule

- 6.55 Baseline risk of hospitalisation assumed in the model by age and risk is summarised in Table 16. The estimation of baseline risk (unadjusted risk in Table 16) was based on AIHW data²⁶. The submission attempted to reverse the impact of vaccination on hospitalisation rates and back-calculate rates expected for an unvaccinated population. The ESC advised that, although the approach may have resulted in an overestimation of baseline hospitalisation rates as there is likely to be some ongoing level of protection due to natural immunity, the approach is consistent with the advice given by ATAGI and was, generally, reasonable.
- 6.56 To back-calculate the acute COVID-19 hospitalisation (ACH) rate for an unvaccinated population, the submission first separated the 18 to 64 years and 65 to 74 years age groups into the various risk groups (SR, HR or IC) by applying a relative risk. The relative risk applied to the HR and IC groups was an assumption. The relative risk applied to the SR group was calculated so that when weighted, the relative risks equal one (i.e., overall, each age group maintains the same risk of ACH, however, ACH by risk groups were estimated).
- 6.57 To remove the impact of vaccination on the population, the submission considered the extent of vaccine coverage in Australia as of 28 June 2023, as reported by the DoHAC²⁷. The submission assumed the vaccine coverage in the HR and IC groups (row “coverage 22-23”) and back-calculated the vaccine coverage that would have been required in the SR group to generate a weighted average of the three risk groups that

²⁵ <https://www.guild.org.au/programs/vaccination-services/nip-vaccinations-in-pharmacy>; and

<https://www.ppaonline.com.au/programs/national-immunisation-program-vaccinations-in-pharmacy-program>

²⁶ <https://www.aihw.gov.au/reports-data/myhospitals/sectors/admitted-patients>

²⁷ <https://www.health.gov.au/sites/default/files/2023-06/covid-19-vaccine-rollout-update-29-june-2023.pdf>

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matched the overall reported coverage. Finally, by using the calculated vaccine coverage in each age group and a vaccine efficacy as reported in the “VE assumed over months 1-6” column in Table 11, the submission back-calculated the risk of ACH in an unvaccinated population in each age and risk group. This approach is consistent with the advice from ATAGI, however, ATAGI noted limitations of this approach:

- Data are relevant to 2022 and 2023, and it is unclear whether rates have since changed;
- COVID-19 deaths that occur outside of a hospitalisation would not be captured;
- COVID-19 deaths in these data relate to a mix of vaccinated and unvaccinated individuals.

Table 16: Summary estimates of baseline risk for acute hospitalised COVID-19 by age and risk groups

	18 to 64 years			65-74 years			75+ years
	SR	HR	IC	SR	HR	IC	All risk
Unadjusted risk ²⁶							
ACH event	0.352%			1.265%			4.128%
ICU	4.383%			5.180%			2.354%
CVS	1.983%			1.864%			0.595%
Death	1.198%			3.409%			5.837%
Adjustment of baseline AIHW risks to back-calculate rates expected for an unvaccinated population							
RR ACH	0.90	1.50	3.00	0.78	1.50	3.00	1.00
ACH by risk group	0.316%	0.528%	1.057%	0.989%	1.898%	3.796%	4.128%
Reported coverage ²⁷	9.15%			40.61%			50.94%
Subgroup proportion	92.09%	4.15%	3.76%	77.49%	18.75%	3.76%	100.00%
Coverage 22-23	3.60%	50.00%	100.00%	28.20%	80.00%	100.00%	50.94%
Efficacy 22-23	55.04%	55.04%	32.27%	55.04%	55.04%	32.27%	55.04%
Adjusted risks in an unvaccinated population							
ACH event	0.322%	0.729%	1.560%	1.171%	3.391%	5.604%	5.667% ^a

a. For 75+ group this was 5.736% in the submission, before the correction in PSCR which resulted in an estimate of 5.667%.

Source: Table 3.4.1 of the submission, and model provided with PSCR .

Abbreviations: ACH = acute COVID-19 hospitalisation; CVS = continuous ventilatory support; HR = high risk; IC = immunocompromised; ICU = intensive care unit; RR = relative risk; SR = standard risk

6.58 The derivation of estimates of VE of raxtozinameran for hospitalisation applied in the model is discussed in paragraphs 6.20 to 6.28 and the estimates of VE are provided in Table 12. As discussed, the submission’s approach to estimation of VE over 12 months for raxtozinameran for hospitalisation included some poorly supported assumptions (e.g., assumptions of ongoing benefit beyond the time horizon examined by the studies, the application of inappropriate weighting of various studies, assumption that evidence from a time when XBB.1.5 was circulating remains applicable).

6.59 Although utility weights were not a substantial driver of cost-effectiveness, the ESC considered the application of disutilities from a French study (Barbut 2019²⁸), which

²⁸ Barbut F., Galperine T., et al. Quality of life and utility decrement associated with *Clostridium difficile* infection in a French hospital setting. *Health Qual Life Outcomes*. 2019;17(1):6. <https://doi.org/10.1186/s12955-019-1081-5>

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estimated utility weights in patients with Clostridium difficile infection, to be inappropriate as it was not a study of COVID-19. The ESC noted that there is a substantial literature base reporting COVID-19-specific utility weights²⁹.

6.60 Premature deaths averted through vaccination for COVID-19 were attributed a discounted QALY loss in the model as follows:

- 15.501 QALYs lost in populations aged 18-64 years;
- 10.365 QALYs lost in populations aged 65-74 years; and
- 5.874 QALYs lost in the population aged 75 years and older.

Although it is possible the submission overestimated the QALY loss for those aged under 75 years, given the life expectancy in each age group was based on the respective general Australian population whereas it is likely that life expectancy of individuals with risk factors, that would be eligible for the vaccine, will be shorter than life expectancy of the average person of that age. The submission presented sensitivity analyses increasing and decreasing the QALY loss payoff by 25% in either direction. The results of the sensitivity analyses showed the model is only marginally sensitive to changes in the QALY loss payoff.

6.61 A summary of the key drivers of the model is presented in Table 17.

Table 17: Key drivers of the model

Description	Method/Value	Impact Weighted Base case: \$ [redacted] ¹ /QALY gained
Baseline risk of hospitalisation	The baseline risk of hospitalisation due to COVID-19 drives the calculation of incremental differences across treatment arms.	High. Changes to the baseline risk of hospitalisation due to COVID-19 result in significant changes to the ICER.
Vaccine efficacy	Derivation is explained in paragraphs 6.20 to 6.28	High, favours raxtozinameran.
Hospitalisation and vaccine administration costs	The costs of hospitalisation and vaccine administration were estimated by AR-DRG codes and an assumption, respectively.	High.
Cost per dose of raxtozinameran	The proposed price per dose of raxtozinameran was \$ [redacted].	High.
Number of doses of raxtozinameran	The maximum number of doses of raxtozinameran according to ATAGI recommendations was assumed in the economic evaluation (biannual dosing assumed where ATAGI advice states these groups “can consider” a dose every 6 months).	High. The ICER is reduced if annual dosing is assumed rather than biannual dosing.

Source: Compiled during evaluation.

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000

6.62 Results for the corrected base case economic evaluation by age and risk category are summarised in Table 18. The ESC noted that the overall weighted ICER was heavily driven by the weighting of the various subpopulations, noting that the submission

²⁹ Mao, Z., Li, X., Jit, M. et al. COVID-19-related health utility values and changes in COVID-19 patients and the general population: a scoping review. Qual Life Res 33, 1443–1454 (2024). <https://doi.org/10.1007/s11136-023-03584-x>

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applied a very low weighting (<0.1%) to the population with the highest ICER, i.e. standard-risk adults aged 18-64 years. The weighted ICER would be substantially higher if a higher utilisation was applied in this group (see Table 19).

Table 18: Summary of incremental base case results (as revised in PSCR)

	18 to 64 years			65-74 years AR			75+ years
	SR	HR	IC	SR	HR	IC	All
Dose frequency	annual	annual	annual (was biannual in submission)	annual	annual (was biannual in submission)	biannual	biannual
Weighting	0.36%	11.56%	20.94%	12.90%	13.24%	3.32%	37.69%
Incremental costs	\$█	\$█	\$█	\$█	-\$█	\$█	-\$█
Incremental QALYs	0.0003	0.0006	0.0006	0.0018	0.0052	0.0065	0.0105
ICER per QALY gained	\$█ ¹	\$█ ²	\$█ ³	\$█ ^{b 4}	DOMINANT ^c	\$█ ⁵	DOMINANT

a. The ICER would be \$155,000 to < \$255,000/QALY with biannual dosing, which is permitted under current arrangements.
 b. The ICER would be \$55,000 to < \$75,000/QALY with biannual dosing, which is permitted under current arrangements.
 c. The ICER would be \$0 to < \$5,000/QALY with biannual dosing, which is permitted under current arrangements.
 Source: Table 5 of the PSCR (Revised base case, including corrections and alignment of doses and uptake with Section 4)
 Abbreviations: HR = high risk; IC = immunocompromised; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SR = standard risk.

The redacted values correspond to the following ranges:

- ¹ \$255,000 to < \$355,000
- ² \$115,000 to < \$135,000
- ³ \$95,000 to < \$115,000
- ⁴ \$25,000 to < \$35,000
- ⁵ \$0 to < \$5,000

- 6.63 The submission calculated a weighted (based on an estimated number of vaccines administered in each population) ICER across all patient age and risk groups. When corrected in the evaluation, the estimate was \$0 to < \$5,000 per QALY gained. However, a weighted ICER is only relevant in the context where NIP-listing is recommended for all of the proposed patient populations. As can be seen from Table 18, the cost-effectiveness of raxtozinameran varied widely by population, with use in some populations appearing to be much more cost-effective than in others. The ICER ranged from indicating that raxtozinameran dominated (more effective and less costly) no additional immunisation in the population aged 75 and above, to more than \$255,000 to < \$355,000/QALY in the standard risk 18–64-year-old population.
- 6.64 The ESC noted that these results were likely underestimated due to multiple concerns as described above. The ESC noted that ATAGI advice indicates that some doses are “recommended” while others are to be “considered” based on the individual’s age and risk status (Table 3) and advised it may be appropriate to consider these populations separately.
- 6.65 Results of sensitivity analyses conducted during the evaluation are presented in Table 19. The results of the economic analysis were particularly sensitive to baseline risk of hospitalisation, vaccine efficacy and costs of raxtozinameran and hospitalisation.

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Table 19: Results of sensitivity analyses using the economic model after correction by evaluator (weighted ICER^a)

Analysis	Incremental costs	Incremental QALYs	ICER	% change from baseline
Base case	\$ [REDACTED]	0.0056	\$ [REDACTED] ¹	-
Baseline risk of hospitalisation and other events including ICU admission, Ventilation and Death				
Risk decreased by 25%	\$ [REDACTED]	0.0032	\$ [REDACTED] ²	+ [REDACTED] %
Risk increased by 25%	-\$ [REDACTED]	0.0088	Dominant	- [REDACTED] %
Risk as per "Adjusted ACH" in Table 16	\$ [REDACTED]	0.0039	\$ [REDACTED] ²	+ [REDACTED] %
Relative risks used as adjustment factors (base case: HR = 1.5; IC = 3.0)				
Low value: HR = 1.125; IC = 2.250	\$ [REDACTED]	0.0053	\$ [REDACTED] ¹	+ [REDACTED] %
High value: HR = 1.875; IC = 3.750	-\$ [REDACTED]	0.0059	Dominant	- [REDACTED] %
Vaccine efficacy				
Vaccine efficacy decreased by 25%	\$ [REDACTED]	0.0042	\$ [REDACTED] ³	+ [REDACTED] %
Vaccine efficacy increased by 25%	-\$ [REDACTED]	0.0070	Dominant	- [REDACTED] %
QALY loss payoff due to premature mortality				
Payoff decreased by 25%	\$ [REDACTED]	0.0042	\$ [REDACTED] ¹	+ [REDACTED] %
Payoff increased by 25%	\$ [REDACTED]	0.0070	\$ [REDACTED] ¹	- [REDACTED] %
QALY utility decrements by health event				
Utility decrements decreased by 25% General ward; 0.0025 ICU admission; 0.0082 CVS; 0.0185	\$ [REDACTED]	0.0056	\$ [REDACTED] ¹	+ [REDACTED] %
Utility decrements increased by 25% General ward; 0.0041 ICU admission; 0.0137 CVS; 0.0308	\$ [REDACTED]	0.0057	\$ [REDACTED] ¹	- [REDACTED] %
Item costs				
Costs decreased by 25% Administration; \$5.25 General ward; \$6,534 ICU admission; \$19,640 CVS; \$36,910 In-hospital death; \$21,028	\$ [REDACTED]	0.0056	\$ [REDACTED] ³	+ [REDACTED] %
Costs increased by 25% Administration; \$8.75 General ward; \$10,889 ICU admission; \$32,734 CVS; \$61,516 In-hospital death; \$35,047	-\$ [REDACTED]	0.0056	Dominant	- [REDACTED] %
Serious adverse event costs (base case = incidence of 0%)				
Incidence of SAEs increased to 0.2%	\$ [REDACTED]	0.0056	\$ [REDACTED] ¹	+ [REDACTED] %
Raxtozinameran cost per dose (base case = \$ [REDACTED])				
Raxtozinameran cost decreased by 25%; \$ [REDACTED]	-\$ [REDACTED]	0.0056	Dominant	- [REDACTED] %
Raxtozinameran cost increased by 25%; \$ [REDACTED]	\$ [REDACTED]	0.0056	\$ [REDACTED] ³	+ [REDACTED] %
Administration cost (base case = \$7)				
Decreased by 25%; \$5.25	\$ [REDACTED]	0.0056	\$ [REDACTED] ¹	- [REDACTED] %
Increased by 25%; \$8.75	\$ [REDACTED]	0.0056	\$ [REDACTED] ¹	+ [REDACTED] %
Increased to the service fee a pharmacist can receive per NIP vaccination; \$19.32	\$ [REDACTED]	0.0056	\$ [REDACTED] ¹	+ [REDACTED] %
Number of doses of raxtozinameran (base case maximum use of raxtozinameran)				

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Analysis	Incremental costs	Incremental QALYs	ICER	% change from baseline
Minimum dosing as per ATAGI recommendations (vaccination every 12 months is "recommended"). Annual utilisation assumed even though instruction states these groups "can consider" a dose every 6 months. 18-64 years IC; 1 dose per year 65-74 years IC; 1 dose per year 65-74 years HR; 1 dose per year	-\$█	0.0053	Dominant	-█%
Additional sensitivity analyses using PSCR revised model				
PSCR base case	-\$█	0.0053	Dominant	n/a
Uptake in SR population aged 18-64 (PSCR base case assumed 0.07% uptake in this group)				
5% uptake in 18-64 years SR population (corresponds to 20.47% weighting for ICER)	\$█	0.0043	\$█ ¹	+█%
10% uptake in 18-64 years SR population (corresponds to 33.98% weighting for ICER)	\$█	0.0036	\$█ ³	+█%
20% uptake in 18-64 years SR population (corresponds to 50.72% weighting for ICER)	\$█	0.0027	\$█ ³	+█%

a. The weightings for each subgroup used for calculation of the weighted ICER are shown in Table 18. Source: Completed during the evaluation based on Table 3.9.2 of the submission, and revised economic model provided with PSCR. ACH = acute COVID-19 hospitalisation; CVS = continuous ventilatory support; HR = high risk; IC = immunocompromised; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; NIP = National Immunisation Program QALY ; quality-adjusted life year; SAE = serious adverse event.

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000

² \$15,000 to < \$25,000

³ \$5,000 to < \$15,000

6.66 Additional concerns noted in the evaluation were as follows:

- 1) Uncertainty in VE, given all studies informing the model are non-randomised, observational studies, which are inherently subject to a high degree of potential for bias. The ESC noted this concern remains.
- 2) An error was identified in relation to the assumed VE for immunocompromised population aged 75 years or above. The base case assumed VE of 55.04% for this subgroup, which was higher than the VE assumed for younger immunocompromised patients (42.81%) which lacked face validity (see paragraph 6.28). It may have been more appropriate to apply a lower VE for the population aged 75 years and above, and/or to model the IC population separately. The PSCR provided a revised estimate of VE for the population aged 75 years and above (paragraph 6.28).
- 3) In addition to the concern in point 2 above, Population 7, i.e. adults aged 75 years or more at any risk of severe acute COVID-19 was modelled as a single population, rather than being split out by SR, HR and IC as for the younger age groups. This means that single estimates of baseline risk and VE are applied in the CUA which may not generate accurate results. The PSCR provided a revised estimate of VE which addressed this concern (paragraph 6.28).
- 4) The economic model applied an uptake of 0.70% in the SR population aged 18-64, which appeared to be an error, as it did not match the financial estimates which

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calculated uptake of 0.07% for this population. The PSCR clarified that the estimate of 0.07% should be applied in the economic model, thereby resolving this discrepancy. The ESC questioned the reliability of the sponsor's estimate for uptake in standard-risk adults aged 18-64 years (0.07%), noting that current reports³⁰ suggested higher uptake in this age group, but these reports did not differentiate between individuals with and without risk factors.

- 5) The submission assumed maximum use of raxtozinameran in populations where the ATAGI recommendations offer a range as set out in Table 4. For example, for the population aged 65 to 74 years, the ATAGI recommendation states that individuals with severe immunocompromise are recommended to receive a vaccine every 12 months and can consider a dose every 6 months. The submission base case assumed all patients in this population receive 2 doses, which resulted in application of the maximum estimated VE for the population over 12 months (Table 12) for every vaccinated individual. This interpretation overestimated the likely utilisation in clinical practice given that the ATAGI advice states that the decision to administer a dose every 6 months, should be based on a risk-benefit assessment for the individual patient, and does not "recommend" 6-monthly dosing for the entire group. The same concern applies for 18–64-year-olds. The PSCR provided a revised cost-effectiveness model (Table 18) which assumed annual vaccination for 18-64 IC group, and 65-74 HR group (whereas biannual vaccination had been assumed in the submission base case). The PSCR stated that biannual dosing will be more effective, but overall less cost effective, than annual vaccination but considered that the overall conclusions on cost-effectiveness remain unchanged.
 - 6) Similar to point 5 above, the submission assumed 100% compliance with all biannual regimens. For example, for the population aged 75 years and above, the ATAGI recommendation states that individuals are recommended to receive a vaccine every 6 months. This assumption overestimated the likely utilisation in this age group, given that perfect compliance is unlikely in clinical practice.
- 6.67 The ESC advised that changes would be required to the economic evaluation. The key advice was:
- 1) The ESC advised that the approach to combining data across various time periods was inappropriate. VE should be adjusted to model 1-3, 4-6, 6-12 months separately, with 4–6-month VE derived from 4–6-month data only, and waning assumed to go to 0 at 12 months (or more conservatively, no VE beyond 6 months). The ESC considered that broad ranges of VE should be tested in sensitivity analyses, particularly if the proposal is for NIP listing of vaccines that are produced

³⁰ Monitoring and reporting on COVID-19, <https://www.health.gov.au/topics/covid-19/monitoring-and-reporting>. COVID-19 vaccination rollout update, <https://www.health.gov.au/resources/collections/covid-19-vaccination-rollout-update>

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using the BNT162b2 platform given the uncertainty of the effectiveness of such vaccines in the future. The estimates of VE over 12 months should also consider waning protection from vaccination and lower effectiveness from changes in circulating variants.

- 2) The ESC advised that better assumptions are required regarding vaccine administration cost given that vaccination was likely to occur across a range of settings (see paragraph 6.54).
 - 3) The ESC advised that the model should be revised to incorporate the effect of antivirals to reflect the reduced risk of hospitalisations due to availability of these therapies. The ESC advised that it would be appropriate for the model to include estimates of the proportion of patients using antivirals in each population and apply the reduced risk of hospitalisation when antivirals are used, at rates as previously accepted by the PBAC. The pre-PBAC response disagreed with this advice (see paragraph 6.49).
 - 4) The ESC advised that economic evaluation for primary courses corresponding to AIH recommendations was required (see paragraph 1.5).
 - 5) The ESC advised that an economic evaluation for paediatric populations was required (paragraph 1.4).
 - 6) Use of COVID-19-specific utility weights should be used (see paragraph 6.59).
 - 7) The ESC noted the heterogeneity in the estimates of cost-effectiveness of raxtozinameran by sub-population. The ESC supported the approach of modelling all populations included in the ATAGI advice to provide an understanding of the range of anticipated cost-effectiveness of the different groups. The ESC noted that accurate estimates of vaccine uptake would be needed as slight changes in weighting could impact the overall cost-effectiveness substantially.
 - 8) It may be appropriate to consider whether it is necessary to consider populations for whom vaccination can be “considered” separately from those in whom vaccination is “recommended” by ATAGI.
- 6.68 The ESC considered that if the sponsor intends to seek PBAC approval for subsequent BNT162b2 vaccines as proposed by the PSCR, then a platform approach to the PBAC consideration would be required. The reimbursement process for future BNT162b2 vaccines would be simplified, if the platform approach is adopted.
- 6.69 The evaluation noted that collection of clinical data for updated COVID-19 vaccines that are released will lag behind the clinical need for the updated COVID-19 vaccines. This is because of the unpredictability of mutations and the unpredictable impact of those mutations of the SARS-CoV-2 virus. The development of updated COVID-19 vaccines is reactive to emerging variants. The PSCR agreed with the evaluation that the rapid evolution of the COVID-19 strains and the time-lag for generating real-world evidence assessing relevant outcomes for severe COVID-19, limits a timely assessment

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of vaccine efficacy for the most recent vaccine adaptation. The pre-PBAC response commented further on this issue, noting that the first RWE reports for BNT162b2 adapted vaccines have tended to be posted in December of each year, however the timeliness of generation of reliable VE estimates are subject to multiple factors including COVID-19 vaccine uptake, COVID-19 epidemiology and incidence, and public health infrastructure to conduct RWE studies. Shifts in these factors have the potential to influence the timing of VE read-outs and outcome reporting.

6.70 The PBAC noted that the submission did not provide estimates of uncertainty for key inputs in the model and considered that plausible ranges would be needed to assess the cost-effectiveness of BNT162b2 vaccines under a platform approach. A summary of key inputs and PBAC comments is provided in Table 20.

Table 20: Summary of key inputs for the economic model and PBAC comments

Population	Aged 18-64 SR	Aged 18-64 HR	Aged 18-64 IC	Aged 65-74 SR	Aged 65-74 HR	Aged 65-74 IC	Aged 75+ AR	PBAC Comment
Doses per year								
PSCR assumption	1	1	1	1	1	2	2	Not consistent with request
ATAGI advice	1	1	2	2	2	2	2	Appropriate for economic evaluation
Baseline risks								
Hospitalisation	0.32%	0.73%	1.56%	1.17%	3.39%	5.60%	5.67%	Point estimates from Table 16, test range in SA
ICU admission	4.38%			5.18%			2.35%	
Ventilation	1.98%			1.86%			0.60%	
Death	1.20%			3.41%			5.84%	
Vaccine efficacy (%)								
VE over 12 months (PSCR doses)	42.81	42.81	21.75	42.81	42.81	32.27	53.31	Point estimates from Table 11, test range in SA
VE over 12 months (ATAGI doses)	42.81	42.81	32.27	55.04	55.04	32.27	53.31	Point estimates from Table 11, test range in SA
Uptake within subgroup, %								
PSCR assumption	0.07	50.00	100	18.87	80.00	100	49.36 ^a	Not consistent with current data
Current utilisation data ^b	10.00	50.00	100	70.00	80.00	100	49.36 ^a	Appropriate for economic evaluation
Increased use in SR groups	20.00	50.00	100	80.00	80.00	100	49.36 ^a	Test in sensitivity analyses

a. Weighted uptake calculated for 75+ population from Excel model, Vaccine!H25.

b. Inputs for 18-64 SR and 65-74 SR edited based on current utilisation data (7 May 2025), which showed higher uptake in the age cohorts (approximately 5% for 18-64 overall population and 24% in the 65-74 overall population) compared with the PSCR estimates (<https://www.health.gov.au/sites/default/files/2025-05/covid-19-vaccine-rollout-update-9-may-2025.pdf>).

6.71 A series of economic model scenarios were prepared to explore the impact of the major uncertainties as outlined in Table 20. The PBAC considered that broad ranges of baseline risks and VE should be tested in sensitivity analyses, particularly if the proposal is for NIP listing of vaccines that are produced using the BNT162b2 platform given the uncertainty of the effectiveness of such vaccines in the future. The results are presented in Table 21, discussion on these scenarios is provided in Section 7.

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Table 21: Economic Model Scenarios

Scenario		Weighted ICER	18 to 64 years			65-74 years			75+ years
			SR	HR	IC	SR	HR	IC	
Doses	ATAGI		1	1	2	2	2	2	2
Weighting, %	PSCR		0.36	11.56	20.94	12.90	13.24	3.32	37.69
Adjusted PSCR model (dosing as per ATAGI advice)	A	\$ 1	\$ 2	\$ 3	\$ 4	\$ 5	\$ 1	\$ 1	Dominant
VE correct calculation error and wane to 0 at 12 months	B	\$ 1	\$ 6	\$ 7	\$ 4	\$ 5	\$ 1	\$ 8	Dominant
Adjust admin cost to \$10.70	C	\$ 8	\$ 6	\$ 3	\$ 4	\$ 5	\$ 1	\$ 1	Dominant
Reduce baseline risks by 25	D1	\$ 9	\$ 10	\$ 4	\$ 2	\$ 3	\$ 9	\$ 9	Dominant
Reduce baseline risks by 50	D2	\$ 11	\$ 12	\$ 10	\$ 13	\$ 2	\$ 5	\$ 11	\$ 14
Reduce VE by 25	E1	\$ 9	\$ 15	\$ 4	\$ 4	\$ 11	\$ 8	\$ 8	Dominant
Reduce VE by 50	E2	\$ 16	\$ 13	\$ 2	\$ 6	\$ 7	\$ 14	\$ 17	\$ 9
Revised weighting scenarios									
Adjust uptake in SR groups to reflect current utilisation ^a			27.59	6.22	11.26	25.75	7.12	1.78	20.27
Weighting, %	F1	\$ 9	\$ 2	\$ 3	\$ 4	\$ 5	\$ 1	\$ 1	Dominant
Adjust uptake in SR groups to increase with NIP ^a			42.04	4.74	8.58	22.42	5.42	1.36	15.45
Weighting, %	F2	\$ 14	\$ 2	\$ 3	\$ 4	\$ 5	\$ 1	\$ 1	Dominant
Multivariate Sensitivity Analyses									
MSA Base Case (A, B, C)	MSA BC	\$ 8	\$ 6	\$ 7	\$ 2	\$ 5	\$ 1	\$ 8	Dominant
MSA BC + D1, E1, F1	MSA 1	\$ 11	\$ 18	\$ 6	\$ 19	\$ 4	\$ 17	\$ 5	\$ 8
MSA BC + D2, E2, F2	MSA 2	\$ 15	\$ 12	\$ 12	\$ 12	\$ 19	\$ 4	\$ 2	\$ 7
MSA BC + D1, E2, F1	MSA 3	\$ 4	\$ 12	\$ 10	\$ 18	\$ 2	\$ 5	\$ 3	\$ 16
MSA BC + D1, E2, F2	MSA 4	\$ 4	\$ 12	\$ 10	\$ 18	\$ 2	\$ 5	\$ 3	\$ 16
MSA BC + D2, E1, F1	MSA 5	\$ 4	\$ 12	\$ 18	\$ 12	\$ 6	\$ 20	\$ 4	\$ 5
MSA BC + D2, E1, F2	MSA 6	\$ 2	\$ 12	\$ 18	\$ 12	\$ 6	\$ 20	\$ 4	\$ 5
MSA BC + D2, E2, F1	MSA 7	\$ 6	\$ 12	\$ 12	\$ 12	\$ 19	\$ 4	\$ 2	\$ 7
MSA BC + D1, E1, F2	MSA 8	\$ 20	\$ 18	\$ 6	\$ 19	\$ 4	\$ 17	\$ 5	\$ 8

a. Corresponding to uptake assumptions in Table 20.

Abbreviations: HR = high risk; IC = immunocompromised; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SR = standard risk

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000; ² \$255,000 to < \$355,000; ³ \$115,000 to < \$135,000; ⁴ \$155,000 to < \$255,000; ⁵ \$55,000 to < \$75,000; ⁶ \$355,000 to < \$455,000; ⁷ \$135,000 to < \$155,000; ⁸ \$5,000 to < \$15,000; ⁹ \$15,000 to < \$25,000; ¹⁰ \$555,000 to < \$655,000; ¹¹ \$75,000 to < \$95,000; ¹² > \$1,055,000; ¹³ \$755,000 to < \$855,000; ¹⁴ \$25,000 to < \$35,000; ¹⁵ \$455,000 to < \$555,000; ¹⁶ \$45,000 to < \$55,000; ¹⁷ \$35,000 to < \$45,000; ¹⁸ \$955,000 to < \$1,055,000; ¹⁹ \$655,000 to < \$755,000; ²⁰ \$95,000 to < \$115,000.

Vaccine cost/administration

6.72 The proposed cost of raxtozinameran per administration is \$[REDACTED]. Depending on an individual's age and risk status, they may require one or two administrations per year according to ATAGI recommendations (March 2025)³¹.

Estimated PBS usage & financial implications

6.73 This submission was considered by the DUSC.

6.74 Key inputs and data sources used by the submission are presented in Table 22.

6.75 The submission used an epidemiological approach to estimate the utilisation and financial implications associated of the requested NIP listing of raxtozinameran for prevention of COVID-19 disease in adults aged ≥ 18 years.

6.76 The submission used a simple approach to estimate the expected utilisation and uptake of raxtozinameran. The data sources used to estimate the financial impact by the submission were:

- Estimation of total eligible population and size of relevant age brackets
 - Australian Bureau of Statistics Population statistics
- Estimation of eligible population by risk group
 - Clark 2020³² to estimate high risk population size
 - MacIntyre 2018³³ to estimate the immunocompromised population size
- Estimation of current uptake
 - DoHAC COVID-19 vaccination data

6.77 The evaluation noted double counting of immunocompromised patients by the submission because immunocompromised patients were included in the estimate of patients at high risk of severe COVID-19 provided by Clark 2020. The evaluation generated revised estimates which removed the proportion of immunocompromised individuals from the pool of high-risk individuals, and noted that changes to the utilisation estimates may impact the cost-effectiveness evaluation, in terms of the weighted ICER. DUSC noted that the study had assumed a consistent rate of immunocompromise (3.76% of the population) regardless of age and considered this

³¹ ATAGI statement on the administration of COVID-19 vaccines in 2025, Issue date: 27 March 2025. <https://www.health.gov.au/resources/publications/atagi-statement-on-the-administration-of-covid-19-vaccines-in-2025?language=en>

³² Clark A., Jit M., et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. *Lancet Glob Health*. 2020;8(8):e1003-e1017. [https://doi.org/10.1016/S2214-109X\(20\)30264-3](https://doi.org/10.1016/S2214-109X(20)30264-3)

³³ MacIntyre R, Costantino V., et al. Influence of population immunosuppression and past vaccination on smallpox reemergence. *Emerg Infect Dis*. 2018;24(4):646-653. <https://doi.org/10.3201/eid2404.171233>

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was not reasonable. A study by Pratt et al. (2021) on the Australian veteran population aged ≥ 70 years reported the proportion of the population with immunocompromise was approximately 10%.

- 6.78 To estimate the uptake rates of raxtozinameran, the submission used Australian COVID-19 vaccination data from the DoHAC (dated 10 October 2024)³⁴. This dataset reports the number of vaccinations received by each age group (18-64 years, 65-74 years and 75+ years) over the last 12 months. The submission did not assume changes in uptake following the listing of raxtozinameran on the NIP, i.e. it assumed a stabilisation of COVID-19 vaccination uptake in terms of the percentage of each cohort being vaccinated, based on the total number of COVID-19 vaccination records in the Australian Immunisation Register (AIR) for the 12 months ending 9 October 2024. However, more recent AIR data suggests a decline in vaccine doses (Figure 6). The submission assumed the listing of raxtozinameran on the NIP will halt the decline (rather than leading to increased uptake rates). The evaluation considered was unclear whether the listing of a new COVID-19 vaccine will lead to changes in the trends regarding vaccination. The DUSC noted the AIR data reported 2.4 million doses were administered in the past 12 months³⁵ and considered the submission's estimated uptake rates to be overestimated.
- 6.79 The DUSC noted 8.8 million doses of the influenza vaccine were administered in 2024³⁶, compared to 2.4 million COVID-19 vaccinations administered in the past 12 months and approximately 4,000,000 to < 5,000,000 doses of raxtozinameran as estimated in the submission. The DUSC considered the differences in terminology between influenza and COVID-19 vaccines and its perception in the community and how this affects uptake. DUSC noted the COVID-19 vaccines are marketed as booster doses, whereas influenza vaccines are marketed as an annual vaccination.
- 6.80 At the time of PBAC consideration, the data for the last 12 months, showed approximately 2.6 million doses had been administered to people aged 18 years and over (as at 7 May 2025)³⁷.
- 6.81 The requested cost per dose of raxtozinameran is \$ [REDACTED]. The number of doses of raxtozinameran assumed per population per year in the financial estimates were:
- Single annual dose
 - Aged 18-64 years at standard risk;
 - Aged 18-64 years at high risk;

³⁴ <https://www.health.gov.au/resources/publications/covid-19-vaccination-vaccination-data-10-october-2024?language=en>

³⁵ <https://www.health.gov.au/topics/covid-19/monitoring-and-reporting>, accessed 4 April 2025.

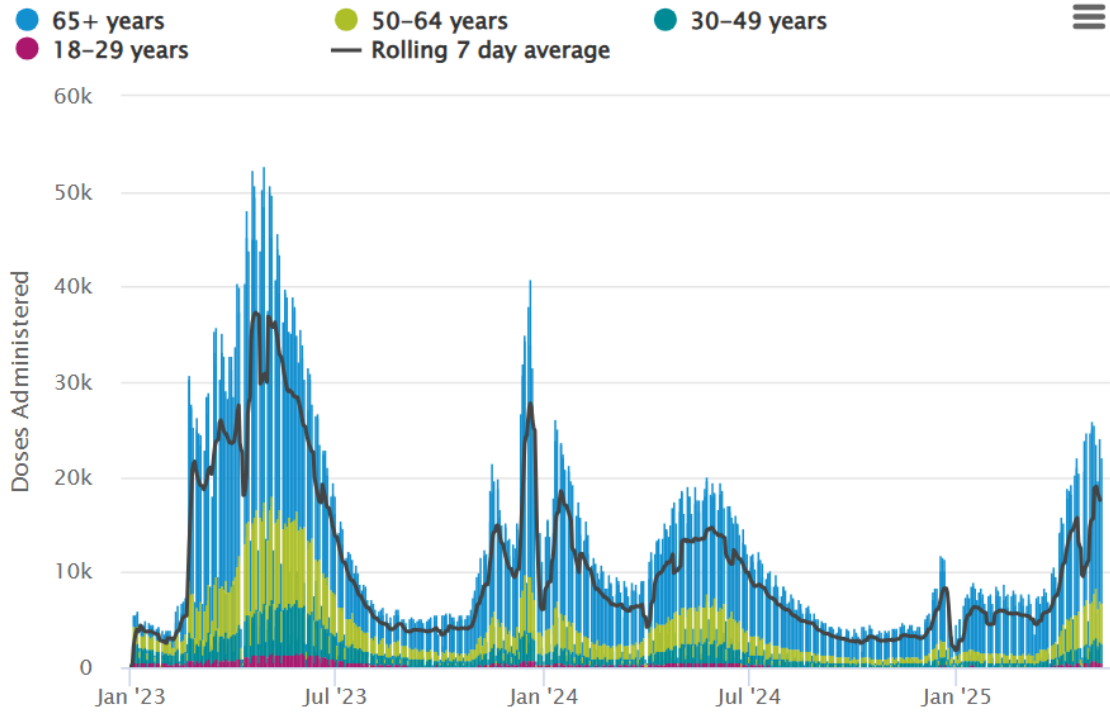
³⁶ <https://www.health.gov.au/resources/collections/influenza-flu-immunisation-data?language=en>, accessed 4 April 2025.

³⁷ <https://www.health.gov.au/topics/covid-19/monitoring-and-reporting>, accessed 9 May 2025.

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- Aged 18-64 years with severe immunocompromise (appears underestimated as biannual dosing is permitted);
 - Aged 65-74 years at standard risk (appears underestimated as biannual dosing is permitted);
 - Aged 65-74 years at high risk (appears underestimated as biannual dosing is permitted);
 - Biannual dose
 - Aged 65-74 years with severe immunocompromise;
 - Aged 75 years or more at any risk of severe acute COVID-19.
- 6.82 As detailed in Table 4, there were inconsistencies across the submission regarding the number of vaccine doses assumed per year and in the extent of uptake by age and risk status. The PSCR stated that no revision of the financial estimates was required. The DUSC noted the submission assumed biannual dosing across several sub-populations and considered it unlikely that full compliance would be observed in clinical practice. For example, the DUSC noted for those aged 65 to 74 years, the ATAGI recommendation states that individuals with severe immunocompromise are recommended to receive a vaccine every 12 months and can consider a dose every 6 months. The submission assumed all patients in this population would receive 2 doses. The DUSC considered utilisation was overestimated by the submission given that the ATAGI advice states that the decision to administer a dose every 6 months should be based on a risk-benefit assessment for the individual patient. The PBAC noted that the submission's financial estimates inappropriately excluded the potential for biannual doses in three of the groups that are permitted this according to current recommendations (paragraph 6.81). The submission inappropriately assumed annual dosing for the 18-64-year-old IC group; the 65-74 SR group; and the 65-74 HR group, for the purposes of the financial estimates.
- 6.83 The DUSC noted raxtozinameran is a pre-filled syringe and commented that it will allow for more opportunistic vaccination due to ease of use and reduce wastage particularly in remote communities, compared with vial formulations.
- 6.84 Regarding the submission's request to list raxtozinameran specifically, the DUSC considered that individuals who have received raxtozinameran or bretovameran through the NCVP may be unwilling to be administered raxtozinameran as a booster given the XBB.1.5 strain is no longer circulating in the community.
- 6.85 The submission assumed [REDACTED] % market share for raxtozinameran. The financial estimates for raxtozinameran may be overestimated, as there are other TGA approved COVID-19 vaccines (e.g., bretovameran).

Figure 6: COVID-19 daily doses administered to adults (as at 7 May 2025)



Source: Australian Immunisation Register as at 7 May 2025, <https://www.health.gov.au/topics/covid-19/monitoring-and-reporting>.
Source: Table 3.9.3 of the submission, updated during the evaluation using the corrected economic model.

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Table 22: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Commentary on the submission	DUSC comments
Eligible population				
Australian population	18-64 years: 16,965,019 65-74 years: 2,559,986 75+ years: 2,228,497	ABS population from UCM workbook	This is appropriate.	This is appropriate.
Proportion of population by risk group	18-64 years SR: Remainder HR: 4.15% IC: 3.76% 65-74 years SR: Remainder HR: 18.75% IC: 3.76% 75+ years SR: Remainder HR: 35.14% IC: 3.76%	Clark 2020 (high risk) and MacIntyre 2018 (immunocompromised)	This appears reasonable. The HR group has been corrected to remove the immunocompromised patients during the evaluation. The submission did not consider the potential overlap when calculating immunocompromised patients and high-risk patients. The definition of high risk according to Clark 2020 includes patients that would be considered immunocompromised.	DUSC noted a study by Pratt et al. (2021) ³⁸ on the Australian veteran population aged ≥70 years had a greater proportion of co-morbidities compared to studies referenced in the submission. DUSC noted this study found approximately 50% of those aged ≥70 years had two or more co-morbidities which was greater than was applied in the submission. DUSC noted the submission assumed 3.76% of individuals (regardless of age) would have immunocompromise. DUSC considered it unreasonable for the submission to apply the same proportion across all age groups and considered the proportion of older age groups with immunocompromise to be underestimated. DUSC noted individuals aged ≥70 years with immunocompromise in the Australian study was approximately 10%.
Treatment utilisation				
Uptake rate (assumed to be constant each year)	18-64 years SR: █████% 18-64 years HR: █████% 18-64 years IC: █████% 65-74 years SR: █████% 65-74 years HR: █████%	Overall vaccinations as a proportion of the total Australian adult population: █████% (2,954,500/21,744,502)	This appears reasonable; however, the submission assumed the uptake rates of vaccination would stabilise following the introduction of raxtozinameran. The data from the DoHAC shows a reducing trend in the number of yearly	DUSC noted the Australian Immunisation Register reported 2.4 million doses were administered in the past 12 months ³⁹ and considered the estimated uptake rates to be overestimated. DUSC considered uptake is dependent upon rates of COVID-19 and its perceived risk in the community.

³⁸ Pratt NL, Kalisch Ellett LM, Andrade AQ, Le Blanc VT, Barratt J, Roughead EE. Prevalence of multiple risk factors for poor outcomes associated with COVID-19 among an elderly Australian population. Aust J Gen Pract. 2021 Jan-Feb;50(1-2):84-89. doi: 10.31128/AJGP-07-20-5546. PMID: 33543170.

³⁹ <https://www.health.gov.au/topics/covid-19/monitoring-and-reporting>

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Data	Value	Source	Commentary on the submission	DUSC comments
	65-74 years IC: [redacted] % 75+ years SR: [redacted] % 75+ years HR: [redacted] % 75+ years IC: [redacted] %		vaccinations. It is unclear whether the introduction of raxtozinameran, a COVID-19 vaccination, would combat the current reducing trends.	DUSC considered vaccine fatigue and its effect on uptake rates. However, DUSC considered factors which contribute to increased uptake include vaccination prior to international travel or where a person or member of their family become immunocompromised.
Doses dispensed	Yr 1: [redacted] 1 Yr 2: [redacted] 1 Yr 3: [redacted] 1 Yr 4: [redacted] 1 Yr 5: [redacted] 1 Yr 6: [redacted] 1	The total number of doses of raxtozinameran estimated to be administered each year. The uptake rates were multiplied by the population projections in the UCM.	This appears reasonable. The calculation is based on the uptake rates	The calculation was appropriate.
Costs				
Proposed medicine	\$ [redacted]	Requested price		
MBS costs	\$7	0.36 services per administration based on MBS item 3 (\$19.60)	This does not appear reasonable. The submission provides limited justification for the administration fee. Pharmacists can receive a service fee of \$19.32 per vaccination.	DUSC agreed with the commentary.

Source: Table 4.1.1 of the commentary on the submission.

Abbreviations: ABS = Australian Bureau of Statistics; DoHAC = Department of Health and Aged Care; HR = high risk; IC = immunocompromised; SR = standard risk; UCM = utilisation and cost model.

The redacted values correspond to the following ranges:

¹ 4,000,000 to < 5,000,000

6.86 Table 23 summarises key inputs to the financial analyses.

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Table 23: Summary of vaccine uptake assumptions by age and risk groups (revised during evaluation)^a

	Description	Age 18-64	Age 65-74	Age 75+	Source / Rationale
A	Total Australian population	16,956,019	2,559,986	2,228,497	Year 2025 values from UCM
B	Proportion of immunocompromised patients	3.76%	3.76%	3.76%	MacIntyre 2018
C	Number of patients immunocompromised	637,546	96,255	83,791	Year 2025 values from UCM =A*B
D	Assumed uptake in the Immunocompromised group	█%	█%	█%	Assumption
E	Sub-total	█ ¹	█ ²	█ ³	=C*D
F	Proportion of high-risk patients (2+ comorbidities)	4.15%	18.75%	35.14%	Clark 2020
G	Number of high-risk patients (based on Clark 2020 values)	█ ⁴	█ ⁵	█ ⁴	Year 2025 values from UCM
H	Revised number of high-risk patients after removing IC patients	█ ⁶	█ ⁷	█ ¹	=G-C
I	Assumed uptake in the high-risk group	█%	█%	█%	Assumption
J	Revised sub-total	█ ⁸	█ ⁷	█ ⁹	Revised total number of high-risk patients =H*I
K	Revised total	█ ¹	█ ⁵	█ ¹	Revised total number of high-risk and IC patients =E+J
L	Number of patients who received a booster dose in the last 12 months	1,000,000	854,500	1,100,000	DoHAC COVID-19 vaccination data – October 2024 ⁴⁰
M	Remaining number of patients who received a booster dose in the last 12 months after high risk and IC patients counted	█ ⁷	█ ⁵	█ ⁵	=L-K
N	Revised standard risk population	█ ¹⁰	█ ¹¹	█ ¹²	=A-C-H
O	Revised uptake in the standard risk group	2.03%	21.69%	31.60%	=M/N

a. Given the potential double-counting of high-risk and immunocompromised individuals; revised estimates were calculated during the evaluation. Rather than considering the calculation of the immunocompromised and high-risk groups to be mutually exclusive, the revised analyses remove the immunocompromised population from the high-risk population. The size of the immunocompromised population across the age groups remained unchanged.

Source: Table 4.3.3 of the submission and prepared during the evaluation.

Abbreviations: DoHAC = Department of Health and Aged Care; IC = immunocompromised; UCM = utilisation and cost model workbook.

The redacted values correspond to the following ranges:

¹ 600,000 to < 700,000

² 90,000 to < 100,000

³ 80,000 to < 90,000

⁴ 700,000 to < 800,000

⁵ 400,000 to < 500,000

⁶ 60,000 to < 70,000

⁷ 300,000 to < 400,000

⁸ 30,000 to < 40,000

⁹ 500,000 to < 600,000

¹⁰ > 10,000,000

¹¹ 2,000,000 to < 3,000,000

¹² 1,000,000 to < 2,000,000

⁴⁰ <https://www.health.gov.au/resources/publications/covid-19-vaccination-vaccination-data-10-october-2024?language=en>

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6.87 Table 24 summarises the overall estimates of extent of use of raxtozinameran and associated financial implications should it be listed on the NIP, as proposed. The submission assumed only the cost of raxtozinameran, and its administration would impact the health budget, if raxtozinameran were to be listed on the NIP. The submission assumed a nominal administration fee of \$7 for each administration of raxtozinameran. The \$7 fee equates to an additional 0.36 Services per script based on the General Practitioner (level A) Schedule Fee of \$19.60 (MBS item 3). The submission anticipated co-administration of raxtozinameran during a pre-existing health care encounter for seasonal influenza immunisation. The exact calculation and source of the 0.36 services per script was not provided.

Table 24: Estimated use and financial implications (corrected during evaluation)^a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Age 18-64 – SR	1	1	1	1	1	1
Age 18-64 – HR	2	2	2	2	2	2
Age 18-64 – IC	3	3	3	3	3	3
Age 65-74 – SR	4	4	4	4	4	4
Age 65-74 – HR	1	1	1	1	1	1
Age 65-74 – IC	5	5	6	6	6	6
Age 75+ - SR	7	7	7	8	8	8
Age 75+ - HR	8	8	8	8	8	8
Age 75+ - IC	5	5	5	5	5	5
Total number of vaccines supplied	9	9	9	9	9	9
Raxtozinameran utilisation (█% market share)	9	9	9	9	9	9
Estimated financial implications of raxtozinameran						
Age 18-64 – SR	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10
Age 18-64 – HR	11	11	11	11	11	11
Age 18-64 – IC	12	12	12	12	12	12
Age 65-74 – SR	13	13	13	13	13	13
Age 65-74 – HR	10	10	10	10	10	10
Age 65-74 – IC	14	14	15	15	15	15
Age 75+ - SR	16	16	16	17	17	17
Age 75+ - HR	17	17	17	17	17	17
Age 75+ - IC	14	14	14	14	14	14
Total Cost to NIP	\$ 18	\$ 18	\$ 18	\$ 18	\$ 18	\$ 18
MBS costs as estimated by submission						
Total services	3	19	19	19	19	19
Cost of additional MBS services	\$ 15	\$ 15	\$ 15	\$ 15	\$ 15	\$ 15

a. Based on revised population estimates presented in Table 23 conducted during the evaluation to remove double-counting of immunocompromised patients.

Source: completed during evaluation using UCM-Release-3-Workbook-Comirnaty_Covid19_Nov 2024.xlsx - Worksheet 3b. Impact – net, MBS costs from Table 4.6.1 of the submission.

Abbreviations: HR = high risk; IC = immunocompromised; SR = standard risk.

The redacted values correspond to the following ranges:

¹ 300,000 to < 400,000

² 30,000 to < 40,000

³ 600,000 to < 700,000

⁴ 400,000 to < 500,000

⁵ 100,000 to < 200,000

⁶ 200,000 to < 300,000

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⁷ 900,000 to < 1,000,000⁸ 1,000,000 to < 2,000,000⁹ 4,000,000 to < 5,000,000¹⁰ \$30 million to < \$40 million¹¹ \$0 to < \$10 million¹² \$60 million to < \$70 million¹³ \$40 million to < \$50 million¹⁴ \$10 million to < \$20 million¹⁵ \$20 million to < \$30 million¹⁶ \$90 million to < \$100 million¹⁷ \$100 million to < \$200 million¹⁸ \$400 million to < \$500 million¹⁹ 700,000 to < 800,000

- 6.88 The corrected total cost to the NIP of listing raxtozinameran was estimated to be \$400 million to < \$500 million in Year 6, and a total of > \$1 billion in the first 6 years of listing.
- 6.89 The submission estimated a cost of approximately \$20 million to < \$30 million in Year 6, and a total of approximately \$100 million to < \$200 million in the first 6 years of listing for MBS costs associated with administration of the vaccine. However, this may be substantially underestimated given that the submission assumed an average cost of only \$7 per administration, and the service fee a pharmacist can receive per NIP vaccination; \$19.32 (see Table 22).
- 6.90 The submission did not present any sensitivity analyses. The submission should have identified market share, uptake rates and the proportion of patients considered high risk or immunocompromised as uncertain inputs. The approach to estimating the utilisation of raxtozinameran was simple with few inputs, however, external data sources and assumptions are inherently uncertain in a rapidly changing Australian context.
- 6.91 The DUSC considers the estimates presented in the submission to be high and overestimated. The main issues raised by DUSC were:
- DUSC considered vaccination uptake would be dependent on the severity of the circulating strain. Based on current rates of vaccination, DUSC considered the estimated uptake rates to be overestimated.
 - DUSC considered the proportion of older individuals with immunocompromise to be underestimated and it was inappropriate to apply the same proportion across all age groups.
 - DUSC considered the submission's assumption of full compliance for those groups eligible for two doses per year to be unlikely in clinical practice.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation for raxtozinameran in relation to the requested National Immunisation Program (NIP) listing for the prevention of COVID-19

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disease caused by the SARS-CoV-2 virus in adults aged ≥ 18 years at increased risk of severe COVID-19 disease. The PBAC advised that further information was required to support appropriate consideration of this submission, including further input from the sponsor, the Australian Technical Advisory Group on Immunisation (ATAGI) and the Department. The PBAC noted that raxtozinameran is currently available to Australians through the National COVID-19 Vaccination Program (NCVP). The PBAC considered it was clinically important to use current vaccines targeting circulating variants, and therefore did not support NIP listing for raxtozinameran. However, the PBAC supported the concept of a platform approach to the PBAC consideration and noted this was also supported by the sponsor and the ATAGI. A platform approach would mean that PBAC advice could apply to future adaptations of the BNT162b2 vaccine, which would be manufactured by Pfizer using the same platform as used for raxtozinameran, after suitable parameters for demonstration of acceptable cost-effectiveness had been determined. In regard to the appropriate populations for NIP listing, the PBAC considered that a restricted program limited to a smaller group of high-risk individuals would reduce health outcomes at the population level compared with current access. The PBAC considered that clinical effectiveness and safety had been demonstrated for raxtozinameran, however the BNT162b2 vaccine platform was not cost-effective at the proposed price. The PBAC advised that a revised proposal was needed from the sponsor to support the cost-effectiveness. The PBAC noted the very high budget impact forecast by the submission and considered that financial risks would need to be managed. The PBAC requested further advice from the Department regarding implementation requirements for a NIP listing for BNT162b2 vaccines based on a platform approach.

- 7.2 The PBAC noted and welcomed the input received from the Lung Foundation Australia and the National Aboriginal Community Controlled Health Organisation (NACCHO) that supported the proposed NIP listing of raxtozinameran, as well as input from an individual that was not supportive. The PBAC acknowledged the crucial role of vaccines in Australia's COVID-19 pandemic response and recovery and noted that vaccines from the BNT162b2 platform have near complete market share in Australia. The PBAC considered that protecting individuals and the broader community from COVID-19 via a national vaccination program remains important. The PBAC noted that COVID-19 was the leading cause of acute respiratory infection mortality in Australia between 2022 and 2024.
- 7.3 The PBAC noted that raxtozinameran is an XBB.1.5-adapted vaccine, whereas the predominant circulating variants are related to the JN.1 variant of SARS-CoV-2. The PBAC noted that bretovameran (Comirnaty® JN.1) was TGA registered in October 2024, and it is currently available to Australians through the National COVID-19 Vaccination Program (NCVP). The PBAC also noted that new adaptations from the BNT162b2 mRNA vaccine platform are anticipated to address evolving variants in the future as part of a global strategy lead by the World Health Organisation (WHO). The PBAC acknowledged the roles of the TGA and the ATAGI to make recommendations

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regarding the use of COVID-19 vaccines in Australia. The PBAC considered it was clinically important to use current vaccines targeting circulating variants, and therefore did not support NIP listing for raxtozinameran as it no longer has a place in therapy. However, the PBAC supported the concept of a platform approach and noted this was also supported by the sponsor and the ATAGI.

- 7.4 The PBAC proposed that it would not need to consider future adaptations of the BNT162b2 vaccines after initial approval unless this was requested by the Department. In the event that a future vaccine adapted from the BNT162b2 platform does not meet the pre-specified requirements for platform approval, then a standard PBAC submission would be required with the submission category determined as per usual practice. In addition, the PBAC may recommend a review of cost-effectiveness post-listing to ensure that overall cost-effectiveness is not compromised in practice.
- 7.5 The PBAC noted and welcomed the advice from the ATAGI. The PBAC noted this was the first submission to the PBAC from any sponsor, seeking reimbursement of a vaccine for the prevention of COVID-19, but that ATAGI had previously considered numerous COVID-19 vaccines and provided pivotal advice for vaccines available via the NCV. The PBAC noted that ATAGI was supportive of a vaccine platform approach for BNT162b2 vaccines. Following the initial inclusion of a BNT162b2 vaccine on the NIP, ATAGI does not consider that, in the majority of cases, a full evaluation of subsequent strain updates is required. The ATAGI advised that in general, approval by the TGA is adequate for the consideration of the ongoing benefit-risk of a vaccine. ATAGI proposed that its role for subsequent strain updates would include:
- Communicating the availability of new TGA approved vaccine strains;
 - Communicating when historical vaccine strains are no longer likely to provide adequate protection against current circulating virus strains;
 - Responding to additional information provided by the Department or sponsors that may result in an update to the ATAGI or AIH advice.

Such advice would be communicated through annual ATAGI COVID-19 advice, and/or via updates to the AIH, and would generally not require a formal evaluation to be undertaken by ATAGI. The PBAC noted that further details of the process are to be determined by the Department.

- 7.6 The PBAC considered that following approval by the TGA and notification by the ATAGI, a platform approach would allow updated vaccines targeting more recent variants of the virus to be included in the NIP in the timeliest manner, consistent with the shared goal of providing access to the most current COVID-19 vaccines for the Australian community. The PBAC noted that a platform approach would require PBAC advice regarding cost-effectiveness to be applied to future adaptations of the BNT162b2 vaccine, manufactured by Pfizer using the same platform as used for all Comirnaty® vaccines including raxtozinameran and bretovameran. The PBAC noted that further details of the process are to be determined by the Department.

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- 7.7 In regard to the requested populations for NIP listing, the PBAC agreed in principle with the sponsor's request for continuation of current vaccine eligibility criteria, that apply for booster doses for adults under the National COVID-19 Vaccination Program (NCVP). The PBAC noted that a restricted program limited to a smaller group of high-risk individuals would reduce health outcomes at the population level.
- 7.8 The PBAC noted that currently primary course vaccination is recommended for all people aged 18 years and older, and for children aged 6 months and older with medical conditions that may increase their risk of severe disease or death from COVID-19. Current advice for all COVID-19 vaccinations is available in the AIH. Most people require one dose for their primary course. People with severe immunocompromise are recommended two primary doses and can consider a third. Further doses every 6 or 12 months may be recommended based on an individual's age and presence of risk factors for severe disease. The PBAC noted that the submission had focussed on booster doses, however considered it would be important that a recommendation for NIP listing was consistent with the summary of current ATAGI recommendations for COVID-19 vaccination as provided in Table 3. The PBAC noted use of primary doses and paediatric doses would likely each represent a small proportion of the total usage. Lower dose formulations would need to be requested for listing for paediatric populations (3 micrograms for children 6 months to 4 years, and 10 micrograms for children 5 to 11 years).
- 7.9 The PBAC considered the appropriate main comparator was no booster vaccination given that no COVID-19 vaccines are currently included on the NIP.
- 7.10 The PBAC noted there are no randomised controlled trials for raxtozinameran specifically, however at the time of TGA registration, efficacy was inferred using immunobridging studies that compared the immune response elicited by raxtozinameran to that of the original BNT162b2 vaccine, based on an implicit assumption that immune response is a valid surrogate for efficacy.
- 7.11 The PBAC noted that the primary evidence to support the effectiveness of raxtozinameran (estimated VE of raxtozinameran for hospitalisation) was derived from eight observational studies as shown in Table 10 (Antunes 2024, Caffrey 2024, Hansen 2024, Link-Gelles 2024, Monge 2024, Nguyen 2024, Nunes 2024, Tartof 2024). The PBAC noted that pivotal RCTs for the BNT162b2 platform such as Study C459001 for the primary course and Study C4591031 for a third dose were not considered in the submission's estimation of VE, as they did not use raxtozinameran. The PBAC noted that estimates of VE for raxtozinameran against hospitalisation ranged from 49% to 76% in immunocompetent populations, and from 27% to 56% in immunocompromised populations in the period in which XBB.1.5 was predominant, and were lower during the period in which JN.1 was predominant as reported in Table 10 (between 36% and 60% for immunocompetent; and 7% to 27% for immunocompromised). The PBAC noted that the submission provided an analysis intended to estimate VE for people who are immunocompetent vs those who are immunocompromised. The PBAC considered that this analysis had a high degree of

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uncertainty and that, although VE was potentially reduced in people who are immunocompromised, their background risk of severe disease was higher and there was thus greater clinical need for vaccination of these populations.

- 7.12 The PBAC noted that the primary evidence to support the safety of raxtozinameran was not drawn from the eight studies described in paragraph 7.11, as they did not specifically report safety outcomes. Instead, the safety claim for raxtozinameran was supported by 1) safety data including reactogenicity and AE profile of raxtozinameran from Substudy A and Substudy B of Study C4591054; 2) a review of data from the pivotal phase 3 trials and reports of real-world studies with BNT162b2 vaccines, not specifically raxtozinameran; and 3) an overview of five studies examining the long-term safety of BNT162b2 vaccines; and 4) a summary of the sixth Periodic Safety Update Report (PSUR) for BNT162b2 vaccines. The PBAC noted that by the end of the PSUR reporting period, approximately 4.85 billion doses had been distributed worldwide, including original, bivalent, and XBB.1.5-adapted vaccines. The PSUR concluded that based on real-world data and clinical trials, no significant long-term safety concerns warranting changes to regulatory guidance or risk management strategies were found. The PBAC noted that the sponsor is required to submit pharmacovigilance data to the TGA on a regular basis.
- 7.13 The PBAC considered that clinical effectiveness and safety had been demonstrated for raxtozinameran. The PBAC considered that the claim of superior effectiveness compared with no booster vaccination was reasonable, however the magnitude of benefit and the duration of benefit were uncertain given the observational nature of the available evidence and methodological issues regarding estimation of VE in various populations. The PBAC considered that the claim of inferior safety compared with no booster vaccination was reasonable. The PBAC noted that the safety of raxtozinameran was supported by randomised clinical trials and real-world experience with earlier BNT162b2 vaccines.
- 7.14 The PBAC noted that while the clinical evidence informing the estimates of VE, for the purposes of economic modelling, were derived from eight observational studies of raxtozinameran, the submission proposed that its modelled economic evaluation could be applicable to not only raxtozinameran, but also subsequent BNT162b2 vaccines, such as bretovameran. The PBAC noted that the submission had also presented evidence from clinical studies of vaccines from the BNT162b2 platform other than raxtozinameran. The PBAC considered that the additional data supported that raxtozinameran was an appropriate proxy for determining effectiveness of TGA-approved vaccines from the BNT162b2 platform to date and potentially in the future, however this approach further increased the uncertainty of the estimates of vaccine efficacy.
- 7.15 For the economic evaluation, the submission presented a decision-tree analysis comparing the costs and outcomes of annual or biannual doses of BNT162b2 vaccine (raxtozinameran or subsequent) or Placebo (as proxy for “no booster” vaccine) in seven mutually exclusive subgroups of Australian adults, the overwhelming majority

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of whom will have been previously exposed to SARS-CoV-2 through previous immunisation and/or natural infection. The PBAC noted that the key clinical event driving the economic model was acute hospitalisation for COVID-19 with four mutually exclusive levels of severity: general ward care only, admission to an intensive care unit (ICU), continuous ventilation support (CVS) and in-hospital death. Different age groups were assigned different baseline rates of hospitalisation, ICU admission, CVS and in-hospital death based on the available AIHW data. The PBAC noted the ESC's advice that the model structure was generally consistent with models previously considered by the PBAC for COVID-19 therapies.

- 7.16 In regard to the consideration of the cost-effectiveness of raxtozinameran, the PBAC advised that revisions were required to the model, to address the issues raised by the ESC as discussed in paragraph 6.67, where this was possible with the evidence available. The PBAC considered that a cost-effectiveness evaluation intended to represent future BNT162b2 vaccines, would need to consider suitably conservative inputs to overcome the PBAC's concerns around: 1) the uncertainty of the applicability of current VE estimates to future vaccines; 2) concerns about diminishing cost-effectiveness of COVID-19 vaccines over time, as it was anticipated that circulating variants will continue to evolve and potentially become less pathogenic; and 3) that the level of immunity in the "no booster" arm will increase over time as hybrid immunity continues to increase (due to past vaccination and natural infections). The PBAC considered in order to recommend the platform approach as cost-effective, it would need to be confident of future cost-effectiveness for scenarios where the incidence of COVID-19 hospitalisations is lower and the vaccine is less effective than was proposed in the submission.
- 7.17 The PBAC noted that the ICERs for the PSCR model, once adjusted to be consistent with ATAGI advice regarding the number of doses, ranged from dominant for the 75+ AR group to \$255,000 to < \$355,000/QALY for the 18-64 SR group. Applying the weightings across the seven populations proposed in the submission results in an estimated ICER of \$0 to < \$5,000/QALY. However, the PBAC noted revising the weightings to reflect current uptake in the SR groups, increased the weighted ICER to \$15,000 to < \$25,000/QALY (Table 21).
- 7.18 The PBAC noted that the estimates of baseline risk of hospitalisation (i.e. the risk without vaccination) were based on AIHW data in 2022-2023 which was then increased to reverse the impact of vaccination. The PBAC noted that the estimates were inherently uncertain, and as expected, varied substantially across the different populations: from 0.322% in the 18-64 SR group to 5.667% in the 75+ AR group (after correction in the PSCR; Table 16). The PBAC further noted that the baseline risk in the proposed circumstances of use may change substantially over time, reflecting the characteristics of circulating SARS-CoV-2 variants, and the potential increase in hybrid immunity (due to past vaccination and natural infections). The PBAC noted that the model did not consider the potential impact of antiviral therapies for COVID-19 on risk of hospitalisation. The PBAC noted that with a 25% or 50% reduction in the baseline

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risk of hospitalisation, the weighted ICER increased from \$0 to < \$5,000 to \$15,000 to < \$25,000/QALY and \$75,000 to < \$95,000/QALY, respectively.

- 7.19 The PBAC noted that the submission estimated VE of raxtozinameran for hospitalisation based on outcomes from 8 observational studies. The PBAC agreed with the ESC that the submission's approach to estimation of VE over 12 months to be inappropriate, particularly the approach to pooling of results from different time periods. The PBAC considered the VE estimated inherently uncertain due to:
- Being source from non-randomised evidence with a wide range of estimates across the different studies;
 - Incorporating assumptions regarding changes in the circulating strains;
 - Assuming efficacy beyond the follow-up period of the studies. The PBAC noted a linear decline in VE was assumed from 7 months and that this resulted in residual VE at 12 months. The PBAC considered that efficacy over 12 months was uncertain and residual VE at 12 months was not supported;
 - In the context of considering the vaccine platform, it being unknown whether future vaccines (including bretovameran) would perform equally well.
- 7.20 The PBAC noted that with a 25% or 50% reduction in the VE the weighted ICER increased from \$0 to < \$5,000 to \$15,000 to < \$25,000/QALY and \$45,000 to < \$55,000/QALY, respectively (Table 21).
- 7.21 The PBAC agreed with the ESC that administration costs were underestimated in the economic analysis (paragraph 6.54). The PBAC noted that adjusting administration costs to \$10.70 assuming 30% of doses administered in pharmacies increased the weighted ICER from \$0 to < \$5,000 to \$5,000 to < \$15,000/QALY (Table 21).
- 7.22 The PBAC considered a range of multivariate sensitivity analyses. In these analyses the model provided with the PSCR was revised to (i) reflect annual or biannual dosing for each group according to the dosing permitted by ATAGI advice (including doses that may be considered; row A in Table 21); (ii) correct the calculation of VE so that estimates from different time periods were not combined, and the VE wanes to 0 at 12 months (row B in Table 21); and (iii) revised the administration cost to \$10.70 (row C in Table 21). The PBAC noted with a 25% reduction in both baseline risk and VE, and weightings to reflect current uptake in the SR groups, the ICER increased to \$75,000 to < \$95,000/QALY (MSA 1 in Table 21). If the baseline risk is reduced by 50% (rather than 25%) the ICER increased to \$155,000 to < \$255,000/QALY, or if the VE is reduced by 50% (rather than 25%) the ICER increased to \$155,000 to < \$255,000/QALY (MSA 3 in Table 21). If the baseline risk and VE are both reduced by 50%, the ICER increased to \$355,000 to < \$455,000/QALY (MSA 7 in Table 21). Overall, the PBAC considered that these results exceeded the value that could be considered cost-effective. The PBAC considered that the weighted ICER that would define acceptable cost-effectiveness should be no greater than \$15,000/QALY. The PBAC noted that cost-effectiveness may vary annually and therefore may be above or below the base

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- case result for a single calendar year but also noted that it needs to be confident that the vaccine is cost-effective in the majority of years in the future.
- 7.23 Based on the discussion and analyses presented in paragraphs 7.16 to 7.22, the sponsor should provide a revised proposal which provides the PBAC confidence that the platform will be cost-effective and likely to remain cost-effective in most future years, including if considered across a cycle of many years.
- 7.24 The PBAC noted that the cost-effectiveness (and hence cost-effective price) varied widely across the different populations (paragraph 7.17) and considered that the risk of increased use in the less cost-effective populations should be managed. The PBAC considered that provided the price reflected current expected use across the different populations, it may be appropriate for the risk of use changing over time to be managed separately. The PBAC considered that the sponsor together with the Department should determine an appropriate mechanism to manage the risk and this should be provided with the revised cost-effectiveness proposal. The PBAC asked the Department to provide advice on an appropriate mechanism to manage this risk (see paragraph 7.26). The PBAC noted that the submission assumed an uptake rate in the 18-64 year old SR group that was unreasonably low (0.07%), and considered any revised base case should assumed uptake in the 18-64 SR group that better reflects current vaccine utilisation data (approximately 10% in 18-64 SR, and 70% in 65-74 SR groups; Table 21).
- 7.25 The PBAC considered that the estimated budget impact was extremely high at the proposed price. The PBAC noted that the total cost to the NIP of listing raxtozinameran was estimated to be > \$1 billion in the first 6 years of listing (after correction during evaluation). Total costs to MBS associated with the administration of vaccine were estimated to be approximately \$100 million to < \$200 million in the first 6 years of listing, although these were considered underestimated. The PBAC considered the estimated utilisation uncertain, because vaccination uptake in practice would vary based on rates of COVID-19 infection and its perceived risk in the community. The PBAC noted recent utilisation data showed seasonal peaks and troughs as shown in Figure 6. The PBAC considered this pattern would likely continue, and that as vaccine uptake may vary on an annual basis, the cost to Government may be higher or lower than forecast in a given year, but overall the total estimates over six years should be more robust. The PBAC noted the revised proposal from the sponsor should include revised financial estimates, and that for each subpopulation where biannual dosing is permitted, the number of annual and biannual doses should be estimated, rather than assuming all annual or all biannual, as was done in the submission (see paragraph 6.82). The PBAC asked the Department to provide advice on an appropriate mechanism to manage the risk that utilisation may vary substantially from year to year.
- 7.26 With regard to further input from the Department, the PBAC sought further advice from the Department on the transition plan for NCVP to NIP, including specific advice in relation to defining a recommendation for BNT162b2 vaccines for the legislation

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that underpins the NIP (the National Health (Immunisation Program — Designated Vaccines) Determination 2014 (No. 1). The PBAC noted that further details of the process are to be determined by the Department. Secondly, the PBAC noted there were risks that would need to be managed and required advice from the Department, and asked the Department to provide advice in regard to management of risks that may be relevant to a recommendation for BNT162b2 vaccines including overall financial risk, and changes in distribution amongst patient populations (see paragraph 7.25 and 7.24, respectively). The PBAC asked the Department provide advice on these areas, to both the sponsor and the PBAC, to support further consideration of the submission.

7.27 With regard to further input from the sponsor, the PBAC requested a written proposal with the following approach for BNT162b2 vaccines:

1) Platform assessment – the PBAC considered it would be appropriate for the sponsor to request NIP listing for vaccines from BNT162b2 platform. The sponsor would need to specify the details for each relevant vaccine (e.g. individual brand names and formulations) and provide evidence of TGA registration for each pack type proposed for NIP listing. The PBAC considered it would be informative for the sponsor to provide an update on any plans for further adapted vaccines underway currently (if any). The sponsor is asked to confirm its commitment to communicate with the Department, the TGA, and ATAGI in a timely manner, with the intent to provide the most up-to-date COVID 19 vaccine to Australians through the NIP.

2) Vaccine eligibility – the PBAC considered it would be appropriate for the sponsor to request NIP listing as per current NCVP access, including paediatric doses and primary doses, and include doses that are either recommended or may be considered, consistent with current ATAGI advice.

3) Economic model – The PBAC considered that revisions were required to the economic model as discussed in paragraph 7.23. As discussed above, the revised proposal should utilise inputs that would provide confidence that the platform will be likely to remain cost-effective in future years. The written proposal should include justification for a proposed price for paediatric doses and primary doses, noting these were not assessed in the current submission.

4) Financial estimates – The PBAC requested revised financial estimates including paediatric doses and primary doses, and also to address the concerns discussed in paragraph 7.24.

7.28 With regard to further input from the ATAGI, the PBAC noted that additional advice would be sought from ATAGI after receipt of a written proposal from the sponsor, to ensure that ATAGI's input was considered for the proposed platform approach for PBAC consideration for BNT162b2 vaccines.

Outcome:

Deferred

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

Pfizer welcomes the PBAC's acknowledgement of the continued burden of COVID-19 and a pragmatic approach to consider Comirnaty® (BTN162b2) as a platform for listing.

Despite the considerable changes requested by the PBAC within the Minutes, Pfizer hopes that the PBAC deferral can be swiftly resolved in collaboration between the Department of Health, Disability & Aging, ATAGI, the PBAC and Pfizer, to achieve a smooth transition to the NIP.