Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Comirnaty Omicron XBB.1.5

Active ingredient/s: Raxtozinameran

Sponsor: Pfizer Australia Pty Ltd

February 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
BNT162b2	Drug development code for Comirnaty Original vaccine (tozinameran)
CMI	Consumer Medicines Information
COVID-19	Coronavirus disease 2019
CPD	Certified Product Details
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
EMA	European Medicines Agency (European Union)
EU	European Union
GFP	Green fluorescent protein
GMP	Good Manufacturing Practice
LNP	Lipid nanoparticles
mRNA	Messenger ribonucleic acid
NAb	Neutralising antibody
PI	Product Information
PSUR	Periodic safety update report
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
WHO	World Health Organization

Product submission

Submission details

Type of submission:	Major variation (update in strain) and new formulation
Product name:	Comirnaty Omicron XBB.1.5
Active ingredient:	Raxtozinameran
Decision:	Approved
Date of decision:	6 October 2023 and 21 December 2023
Date of entry onto ARTG:	9 October 2023 and 22 December 2023
ARTG number:	419330, 419331, 419332, 419370, 419371, 419372 and 428610
, *Black Triangle Scheme*	Yes
for the current submission:	
Sponsor's name and address:	Pfizer Australia Pty Ltd Level 17 151 Clarence Street Sydney, NSW, 2000
Dose form:	Suspension for injection and concentrated solution for injection
Strengths:	3 µg/0.3 mL, 3 µg/0.2 mL, 10 µg/0.3 mL, 10 µg/0.2 mL, and 30 µg/0.3 mL
Containers:	Single dose vial and multidose vial
Pack sizes:	10 and 195
Approved therapeutic use for the current submission:	*Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 6 months of age and older.* *The use of this vaccine should be in accordance with official recommendations.*
Route of administration:	Intramuscular

Dosage:

Strength and age of individual	Volume of each dose	Dose schedule for primary series and additional dose(s)
3 µg per dose 6 months to <5 years	0.2 mL 0.3 mL	Primary series: 3 doses Doses 1 and 2: at least 3 weeks apart Dose 3: at least 8 weeks after second dose
10 µg per dose 5 to <12 years 30 µg per dose	0.2 mL 0.3 mL 0.3 mL	Primary series: 2 doses at least to 21 days (preferably 3 weeks) apart Additional dose(s): at least 3 months after a previous dose

12 years and older		

Primary series, when clinically indicated, can be given to the individuals such as those who are vaccine-naïve and immunocompromised.

The decision when and for whom to administer Comirnaty Omicron XBB.1.5 should be made based on available vaccine safety and effectiveness data (see Sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties of the Product Information), in accordance with official recommendations.

For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category: B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Pfizer Australia Pty Ltd (the sponsor) to register Comirnaty Omicron XBB.1.5 (raxtozinameran) 3 µg/0.3 mL, 3 µg/0.2 mL, 10 µg/0.3 mL, 10 µg/0.2 mL, and 30 µg/0.3 mL, suspension for injection, single dose vial and multidose vial for the following proposed strain update and new formulations:[1]

> *To supply Comirnaty monovalent COVID-19 vaccines adapted to latest dominating SARS-CoV-2 Omicron XBB.1.5 strain.*

[1] This is the original dose regime proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA.

Table 1: Sponsor proposed formulations

Product name	ARTG
COMIRNATY (tozinameran) COVID-19 VACCINE 30 micrograms/0.3 mL suspension for injection vial	377110
COMIRNATY (tozinameran) COVID-19 VACCINE 10 micrograms/0.2 mL concentrated suspension for injection vial	377111
COMIRNATY (tozinameran) COVID-19 VACCINE 3 micrograms/0.2 mL concentrated suspension for injection vial	393433
COMIRNATY Omicron XBB.1.5 (raxtozinameran) COVID-19 VACCINE 30 micrograms/0.3 mL suspension for injection multidose vial	New
COMIRNATY Omicron XBB.1.5 (raxtozinameran) COVID-19 VACCINE 30 micrograms/0.3 mL suspension for injection vial	New
COMIRNATY Omicron XBB.1.5 (raxtozinameran) COVID-19 VACCINE 10 micrograms/0.2 mL concentrated suspension for injection vial	New
COMIRNATY Omicron XBB.1.5 (raxtozinameran) COVID-19 VACCINE 10 micrograms/0.3 mL suspension for injection multidose vial	New
COMIRNATY Omicron XBB.1.5 (raxtozinameran) COVID-19 VACCINE 10 micrograms/0.3 mL suspension for injection vial	New
COMIRNATY Omicron XBB.1.5 (raxtozinameran) COVID-19 VACCINE 3 micrograms/0.2 mL concentrated suspension for injection vial	New

The sponsor has applied for approval for strain update for currently registered Comirnaty (monovalent, original) to the monovalent COVID-19 vaccine raxtozinameran (Comirnaty Omicron XBB.1.5) in lipid nanoparticles (LNP). The Omicron XBB.1.5 vaccine is indicated (proposed) for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.

The messenger ribonucleic acid (mRNA) of the Omicron XBB.1.5 variant is manufactured using the same processes as for the original monovalent vaccine (BNT162b2).

The sponsor initially proposed registration for six formulations. However, quality data has only been provided for the 10 µg per dose (single dose vial with light blue cap) and 30 µg per dose (multidose vial with dark grey cap) and the data for remaining formulations will be submitted at a later stage.[2] For this reason, the decision for this application will be divided in to two stages.

Condition

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly and globally since its emergence, causing coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared that the outbreak constituted a public health emergency of international concern on 30 January 2020 and declared the outbreak to be a pandemic on 11 March 2020.

The rise of the COVID-19 Omicron subvariant XBB.1.5 is the product of a potent mix of mutations that make it easier to spread broadly, including among those who have been previously infected or vaccinated. That means there are higher chances for reinfection or breakthrough infections.

Since the COVID-19 Omicron variant became the world's dominant strain, it has mutated into different subvariants. First it was BA.1, then it was the BA.5 Omicron subvariant. It eventually mutated into BQ.1 and BQ.1.1.[3]

The Omicron XBB.1.5 strain is derived from the Omicron BA.2 subvariant. It is part of the XBB family of variants and contains more mutations to evade immunity than other variants seen so

[2] Sponsor clarification: Sponsor submitted quality data for all six presentations proposed with the initial submission.

[3] American Medical Association (AMA) XBB.1.5 Omicron Subvariant: Questions Patients May Have, 2 February 2023. Available at: https://www.ama-assn.org/delivering-care/public-health/xbb15-omicron-subvariant-questions-patients-may-have.

far. The XBB.1.5 subvariant has a mutation that is believed to help the virus bind to cells, becoming more transmissible.[3]

Currently circulating mutated SARS-CoV-2 Omicron subvariants are posing challenges for current vaccination strategies.

Comirnaty XBB.1.5 Vaccine

Raxtozinameran is a single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding deoxyribonucleic acid (DNA) templates, encoding the viral spike protein of SARS-CoV-2 subvariant strain Omicron XBB.1.5.

Regulatory status

The TGA has approved the full registration of Comirnaty (tozinameran) on the 14 July 2023.[4]

At the time the TGA considered this submission for Comirnaty Omicron XBB.1.5 (raxtozinameran), a similar submission had been approved in European Union (EU) on 31 August 2023, United States of America on 11 September 2023 and Canada on 28 September 2023.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Data were provided as a rolling submission. Under normal circumstances, TGA's assessment (for both provisional and general registration) begins once all information to support registration is available. As part of the Department of Health and Aged Care's response to the pandemic, the TGA has agreed to accept rolling data for COVID-19 vaccines and treatments, to enable early evaluation of data as it becomes available.

Stage I decision (AUSR R 419330 and 419371)

Description	Date
Submission dossier accepted and first round evaluation commenced	23 August 2023
Evaluation completed	5 October 2023
Delegate's[5] Overall benefit-risk assessment and request for Advisory Committee advice	29 September 2023

[4] AusPAR for Comirnaty transition of provisional registration to full registration. Available at https://www.tga.gov.au/resources/auspar/auspar-comirnaty-covid-19-vaccine

[5] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Description	Date
Sponsor's pre-Advisory Committee response	3 October 2023
Advisory Committee meeting	4 October 2023
Registration decision (Outcome)	6 October 2023
Administrative activities and registration on the ARTG completed	9 October 2023
Number of working days from submission dossier acceptance to registration decision*	32 days

*Statutory timeframe for standard submissions is 255 working days

Stage II decision (AUST R 419331, 419332, 419370, 419372 and 428610)

Description	Date
Submission dossier accepted and first round evaluation commenced	23 August 2023
Evaluation completed	21 December 2023
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	21 December 2023
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	21 December 2023
Administrative activities and registration on the ARTG completed	22 December 2023
Number of working days from submission dossier acceptance to registration decision*	86

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

Stage I decision (AUST R 419330 and 419371)

Due to timeframe constraints, the Delegate noted the following two presentations (total 6 formulations are proposed by the sponsor, see Table 1) are prioritised to ensure age groups: 12 years and older and 5 to younger than 12 years will be covered.

Table 2: Comirnaty formulation for AUST R 419330 and 419371 products

Age group	12 years and older	5 to <12 years
AUST R	419330	419371
Cap and Label colour code	Dark Grey	Light Blue
Pharmaceutical form	Suspension for injection	Suspension for injection
Strength per dose	30 µg (0.3 mL dose)	10 µg (0.3 mL dose)
Fill volume	2.25 mL	0.48 mL
No. of doses per vial	6	1
Dilution	Do not dilute	Do not dilute

The Delegate noted that Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 Vaccine 30 µg/0.3 mL suspension for injection multidose vial presentation is based on ARTG entry 377110 (identical formulation);[6] while the Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 Vaccine 10 µg/0.3 mL suspension for injection represents a new single dose vial presentation, both presentations not requiring dilution prior to use.

Comparability

The quality evaluation commented that since the manufacturing processes remains unchanged for both the drug substance (DS) and drug product (DP) such that processes are previously validated (linear DNA template, DS and DP), the sponsor has provided a single confirmatory batch of DS (HD1999) and four confirmatory lots of DP (HD9835; HE0781; HE0786; and HE2391) manufactured at one approved manufacturing facility on approved manufacturing line(s).

The quality evaluation noted that the four DP lots represent the different product presentations: HD9835 - 0.48 mL fill, 30 µg dose; HE0781 - 1.3 mL fill, 10 µg dose (dilute to use); HE0786 - 0.4 mL fill, 3 µg dose (dilute to use); and HE2391 - 0.48 mL fill, 10 µg dose (ready to use). Given

[6] ARTG entry for Comirnaty (tozinameran) COVID-19 vaccine 30 µg/0.3 mL suspension for injection vial. Available at: https://www.tga.gov.au/resources/artg/377110.

that the manufacture of the remains unchanged, the DP lots are considered representative of the DP manufacturing process and are acceptable.

Drug substance

The quality evaluation commented that batch analysis for the single Omicron XBB.1.5 DS batch HD1999 met the acceptance criteria in place at the time of release. Since the manufacturing process of the DS is unchanged from the previous Original and Omicron DS manufacturing, the single DS release data indicate that the DS manufacturing process remains capable of consistently manufacturing DS meeting the required quality attributes.

Drug product

The quality evaluation commented that batch analysis for the four Omicron XBB.1.5 DP batches: HD9835; HE0781; HE0786; and HE2391 met the acceptance criteria in place at the time of release. Since the manufacturing process of the DP is highly similar to the previous Original monovalent and Omicron bivalent products, the release data indicate that the DP manufacturing process remains capable of consistently manufacturing DP meeting the required quality attributes.

While it is usual practice to require three batch analytical data for DS and DP to confirm batch-to-batch consistency, and to demonstrate there is no significant drift in quality attributes, the provided data is considered acceptable. Since the manufacturing processes remain unchanged and the control of the DS and DP remain unchanged with the exception of tests for identity, the control strategy is considered to be maintained as demonstrated through the available batch analysis data.

The quality evaluation commented that post approval, the sponsor should provide batch analysis data for additional DS and DP batches manufactured at the commercial scale once they become available to support batch-to-batch consistency.

Stability

Drug substance

The quality evaluation commented that no new stability data was submitted for the Omicron XBB.1.5 DS at the time of evaluation. The sponsor proposes a commercial shelf-life of the Omicron XBB.1.5 DS of:

- Six months when stored at the intended storage condition of -20±5°C in ethylene vinyl acetate bags.

The shelf-life is based on the currently available results of primary stability studies conducted on commercial Original and Omicron (BA.4/5) DS batches corresponding with the approved shelf-life of the Original (tozinameran) DS and is acceptable since they are highly similar.

Post-approval commitment

The sponsor is requested to provide the results from ongoing stability studies performed on Omicron XBB.1.5 DS lots when stored at -20±5°C and 5±3°C for each time point in accordance with the stability testing protocols to confirm the shelf life of six months stored at -20±5°C.

Drug product

The quality evaluation commented that no new stability data was submitted for the Omicron XBB.1.5 DP at the time of evaluation. The sponsor proposes a commercial shelf-life of the Omicron XBB.1.5 DP of 18 months when stored at -90°C to -60°C.

However, the shelf-life for all Comirnaty products registered in Australia was recently extended to 24 months storage at -90°C to -60 °C. The shelf-life of 24 months is based on extensive stability data on the Original PBS/Sucrose and TRIS/Sucrose Comirnaty (Original) DP where up to 24 months stability data is available for PBS/Sucrose DP lots and primary stability data is available for TRIS/Sucrose DP lots when stored at -90°C to -60°C.

Given the manufacturing processes for the DP remain unchanged and the specifications for the control of the DP are identical (except for identity methods), it is acceptable to leverage the shelf-life for the Omicron XBB.1.5 DP from the extensive stability data available on Original (PBS/sucrose and Tris/sucrose formulations).

Based on the above, the recommended shelf life and storage conditions are:

- Shelf life: 24 months from the date of manufacture
- Storage condition: -90°C to -60°C

Container safety

No updated information was submitted for the container closure system and the container safety evaluation indicated that this was acceptable, and no further evaluation was required.

Endotoxin

An endotoxin secondary evaluation was not required since it is the same formulation as those already submitted and the change relates to ribonucleic acid (RNA) sequence(s) used only.

Infectious disease/viral safety

A secondary evaluation was conducted to evaluate the infectious disease safety of the DS and DP and concluded that sufficient evidence has been provided to demonstrate that the risks related to the presence of adventitious agents in the manufacturing of Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 Vaccine have been controlled to an acceptable level.

Microbiology (sterility)

A secondary evaluation was conducted to evaluate the sterility aspects and concluded there are no objections from a microbiological perspective for the proposed product presentations.

Conclusions and recommendations

There are no significant issues identified from the quality evaluation of the submitted data that would indicate the product should not be fully registered on the basis of quality, or safety-related issues arising from the quality of the product. The manufacturing quality information submitted by the sponsor support the full registration of:

- Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 Vaccine 30 µg/0.3 mL suspension for injection multidose vial (AUST R 419330)
- Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 Vaccine 10 µg/0.3 mL suspension for injection single dose vial (AUSTR R 419371)

The quality evaluation has advised that the Delegate should review the Proposed Conditions of Registration to ensure the product is fully compliant with all the previously mentioned instruments before release into the market.

Post approval commitment

The sponsor should complete the following post-approval commitments within the stated timeframe (see Table 3 below).

Table 3: Post approval quality commitments

Description	Due date
GMP[7] clearance of manufacturing sites: All relevant manufacturing sites require approved and current GMP clearances prior to Australian supply. A commitment is required from the sponsor that they maintain the validity of all manufacturer GMP clearances for the duration of product supply to Australia. Additionally, that adherence to the conditions of GMP Clearance approval is upheld.	No date
Post-approval stability protocol and stability commitment: Provide the results from ongoing stability studies performed on Omicron XBB.1.5 DS lots when stored at -20 ± 5°C and 5 ± 3 °C for each time point in accordance with the stability testing protocols to support the shelf-life of the DS. Provide the results from ongoing stability studies performed on XBB.1.5 variant DP lots when stored at -90 to -60 °C and 5 ± 3 °C for each time point in accordance with the stability testing protocols to support the shelf-life of the DP.	First quarter of 2024
Batch analysis: Provide batch analysis data for additional DS and DP batches manufactured at the commercial scale once they become available to support batch-to-batch consistency.	First quarter of 2024

Abbreviations: DP = drug product; DP = drug substance; GMP = Good Manufacturing Practice.

Stage II decision (AUST R 419331, 419332, 419370, 419372 and 428610)

Stage II decision covers assessment of quality data for the final five presentations out of seven, with an additional presentation submitted after the completion of Stage I decision. Table 4 summarises all seven formulations/presentations of Comirnaty Omicron XBB.1.5 evaluated for this submission.

Table 4: Seven presentations of Comirnaty Omicron XBB.1.5

Age group	12 years and older		5 to <12 years			6 months to <5 years	
AUST R	419370	419330	419331	419371	419372	419332	428610
Cap and label colour code	Light Grey	Dark Grey	Orange	Light Blue	Dark Blue	Maroon	Yellow
Pharmaceutical form	Suspension for injection		Concentrate for suspension for injection	Suspension for injection		Concentrate for suspension for injection	

[7] Good Manufacturing Practice (GMP) is a code of standards that describes a set of principles and procedures that when followed helps ensure that therapeutic goods are of high quality.

Age group	12 years and older		5 to <12 years			6 months to <5 years	
Strength per dose	30 µg (0.3 mL dose)		10 µg (0.2 mL dose)	10 µg (0.3 mL dose)		3 µg (0.2 mL dose)	3 µg (0.3 mL dose)
Fill volume	0.48 mL	2.25 mL	1.3 mL	0.48 mL	2.25 mL	0.4 mL	0.48 mL
No. of doses per vial	1	6	10	1	6	10	3
Dilution	Do not dilute		Requires dilution	Do not dilute		Requires dilution	

Comparability

The quality evaluation commented that since the manufacturing processes remains unchanged for both the DS and DP such that processes are previously validated (linear DNA template, DS and DP), the sponsor has provided a single confirmatory batch of DS (HD1999) and four confirmatory lots of DP (HD9835; HE0781; HE0786; and HE2391) manufactured at one approved manufacturing facility on approved manufacturing line(s).

The quality evaluation noted that the four DP lots represent the different product presentations: HD9835 (0.48 mL fill, 30 µg dose), HE0781 (1.3 mL fill, 10 µg dose (dilute to use)), HE0786 (0.4 mL fill, 3 µg dose (dilute to use)), and HE2391(0.48 mL fill, 10 µg dose (ready to use)). Given that the manufacture of the remains unchanged, the DP lots are considered representative of the DP manufacturing process and are acceptable.

Drug substance

The quality evaluation commented that batch analysis for the single Omicron XBB.1.5 DS batch HD1999 met the acceptance criteria in place at the time of release. Since the manufacturing process of the DS is unchanged from the previous Original and Omicron DS manufacturing, the single DS release data indicate that the DS manufacturing process remains capable of consistently manufacturing DS meeting the required quality attributes.

Drug product

The quality evaluation commented that the batch formula for the 0.1 mg/mL and the 0.033 mg/mL bulk DP was previously evaluated as part of Stage I decision and is applicable for the remaining 5 presentations. It should also be noted that the newly introduced yellow cap presentation (3 µg/0.3 mL) is the same as the light blue presentation (AUST R 419371) approved under Stage I decision.

Stability

Drug substance

The quality evaluation commented that no new stability data was submitted for the Omicron XBB.1.5 DS at the time of evaluation. This was previously discussed as part of Stage I decision and is applicable for the remaining 5 presentations. The sponsor proposed a commercial shelf-life of the Omicron XBB.1.5 DS of:

- 6 months when stored at the intended storage condition of -20±5°C in ethyl vinyl acetate (EVA) bags.

The shelf-life is based on the currently available results of primary stability studies conducted on commercial Original and Omicron (BA.4-5) DS batches corresponding with the approved shelf-life of the Original (tozinameran) DS and is acceptable since they are highly similar.

Post-approval commitment

The sponsor is requested to provide the results from ongoing stability studies performed on Omicron XBB.1.5 DS lots when stored at -20±5°C and 5±3°C for each time point in accordance with the stability testing protocols provided to the TGA (Omicron XBB.1.5 variant) to confirm the shelf life of 6 months stored at -20±5°C.

Drug product

As noted previously in Stage I decision, there was no stability data available at the time of evaluation of the DP. Following the first round of evaluation, the sponsor submitted a limited stability dataset for the XBB.1.5 DP which was evaluated in the second round of evaluation.

One month stability data was available for three DP lots stored at -90°C to -60°C (HD9835; HE0781; and HE0786) and demonstrated comparable stability with the Original monovalent DP at the one-month storage point when stored at the recommended storage condition of -90°C to -60°C.

Since the XBB.1.5 DP is manufactured in an equivalent manner as previously registered Comirnaty products (Original and Bivalent presentations) and at the same manufacturing sites, and only differ in the sequence in the DS, leveraging the shelf-life from previously registered Comirnaty products for the establishment of the shelf-life for the XBB.1.5 DP is acceptable.

The recommended shelf-life for the XBB.1.5 variant DP is:

- 24 months when stored at the long-term storage condition of -90°C to -60°C
- shelf-life also includes an allowance for storage at 5±3°C for up to 3 months, within the 24-month, supporting the subsequent storage conditions of 5±3°C for 10 weeks at the point of use.

Container safety

No updated information was submitted for the container closure system and the container safety evaluation indicated that this was acceptable, and no further evaluation was required.

Endotoxin

An endotoxin secondary evaluation was not required since it is the same formulation as those already submitted and the change relates to RNA sequence(s) used only.

Infectious disease/viral safety

A secondary evaluation was conducted to evaluate the infectious disease safety of the DS and DP and concluded that sufficient evidence has been provided to demonstrate that the risks related to the presence of adventitious agents in the manufacturing of Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine have been controlled to an acceptable level.

Microbiology (sterility)

A secondary evaluation was conducted to evaluate the sterility aspects and concluded there are no objections from a microbiological perspective for the proposed product presentations.

Conclusions and recommendations

There are no significant issues identified from the quality evaluation of the submitted data that would indicate the product should not be fully registered on the basis of quality, or safety-related issues arising from the quality of the product.

The manufacturing quality information submitted by the sponsor support the full registration of:

- Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 30 μg/0.3 mL suspension for injection single dose vial (one dose per vial) (light grey cap – ready to use)
- Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 10 μg/0.2 mL concentrated suspension for injection multidose vial (10 doses per vial) (orange cap – requires dilution)
- Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 10 μg/0.3 mL suspension for injection multidose vial (6 doses per vial) (dark blue cap – ready to use)
- Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 3 μg/0.2 mL concentrated suspension for injection multidose vial (10 doses per vial) (maroon cap – requires dilution)
- Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 3 μg/0.3 mL concentrated suspension for injection multidose vial (3 doses per vial) (yellow cap – requires dilution)

The quality Delegate has reviewed the proposed conditions of registration to ensure the product is fully compliant with all the previously mentioned instruments, before release into the market.

Nonclinical

The nonclinical dossier comprised of two pharmacology studies comparing the immunogenicity of the Omicron XBB.1.5 sublineage-modified vaccines as a primary series (two doses) in naïve mice and a fourth booster dose in BNT162b2 experienced mice. In addition, a study report on distribution and protein expression in mice after injection of a green fluorescent protein (GFP) modified RNA LNP was submitted. No pharmacology protection studies for Omicron XBB.1.5 were submitted. This is acceptable as there are no changes to the original vaccine formulation except for replacement of a serotype strain RNA. All other nonclinical safety studies were covered in the original Comirnaty application.[8]

Immunogenicity

The immunogenicity of COVID-19 monovalent and bivalent XBB.1.5, sublineage-modified vaccines in naïve mice as a primary series is listed below.

The Omicron XBB.1.5 (0.5 μg) sublineage-modified monovalent and bivalent vaccines (Omicron BA.4/5 (0.25 μg) plus Omicron XBB.1.5(0.25 μg)) as a primary two dose series in naïve mice induced higher (19 to 42-fold) neutralising antibody response against Omicron XBB.1.5, XBB.1.16, XBB.1.16.1 and XBB.2.3 compared to bivalent (wild type (0.25 μg) plus Omicron BA.4/5 (0.25 μg)) vaccine. However, the strongest responses were generally observed with the monovalent BNT162b2 XBB.1.5 group (see Table 5 below).

[8] AusPAR for original Comirnaty application. Available at: https://www.tga.gov.au/resources/auspar/auspar-bnt162b2-mrna-comirnaty.

Table 5: Neutralising antibody titres, one month after two doses of monovalent or bivalent vaccine as a primary series

Vaccines	Variants					
	Wuhan	BA.4/5	XBB.1.5	XBB.1.16	XBB.1.16.1	XBB.2.3
NAb titre						
WT-BA.4/5	981	8580	87	182	114	116
XBB.1.5	41	1717	3064	3767	3461	2689
BA.4/5 + XBB.1.5	47	14730	2664	3493	4724	2602
NAb titre ratio						
XBB.1.5	0.04	0.2	36	21	30	23
BA.4/5 + XBB.1.5	0.05	1.7	31	19	42	22

Abbreviation: NAb = neutralising antibody, WT = wild type

The immunogenicity of COVID-19 monovalent and bivalent XBB.1.5 sub lineage-modified vaccines in BNT162b2 experienced mice as a fourth dose booster is listed below.

In BNT162b2 experienced mice, monovalent BNT162b2 XBB.1.5 (0.5 µg) induced four-to-six-fold higher neutralising responses against Omicron sub lineages XBB.1.5, XBB.1.16, XBB.1.16.1 and XBB.2.3 compared to benchmark bivalent BNT162b2 (wild type (0.25 µg) plus Omicron BA.4/5(0.25 µg)), (see Table 6 below).

Table 6: Neutralising antibody titres, one month post fourth dose booster with Omicron XBB monovalent and bivalent vaccines

Vaccines	Variants					
	Wuhan	BA.4/5	XBB.1.5	XBB.1.16	XBB.1.16.1	XBB.2.3
NAb Titre						
WT-BA.4/5	71748	40689	444	733	598	621
XBB.1.5	100108	41055	1800	3766	3456	3020
BA.4/5 + XBB.1.5	74398	54322	775	1523	1046	669
NAb titre ratio						
XBB.1.5	1.4	1.0	4.1	5.1	5.8	4.9
BA.4/5 + XBB.1.5	1.0	1.3	1.7	2.1	2.4	1.1

Abbreviation: NAb = neutralising antibody, WT = wild type

In both the pharmacology studies, none of the XBB sub-lineages tested showed evidence of immune escape. Both monovalent and bivalent containing XBB.1.5 vaccines induced a $CD4^+$ and $CD8^+$ T-cell response. The monovalent XBB.1.5 vaccine showed a higher response than the bivalent variant. Therefore, the XBB.1.5 monovalent vaccine is likely to provide better protection against currently circulating strains as compared to the previously approved variant vaccines.

Distribution and protein expression

A distribution study in mice with LNP containing modified RNA for GFP showed presence of modified RNA and expression of GFP predominantly at the injection site, draining lymph nodes and spleen, with rare observations in the liver. These findings are in line with data submitted in the original application,[8] where distribution studies used modified RNA expressing luciferase.

Recommendation

There are no nonclinical objections to the approval of the Comirnaty Omicron XBB.1.5 monovalent vaccine.

Clinical

No clinical data was submitted with this application.

Risk management plan

No risk management plan (RMP) has been provided by the sponsor and it is acceptable at this stage. The changes proposed in this application are not significant from an RMP perspective.

Risk-benefit analysis

Delegate's considerations

This is a major and minor variation application to update the currently approved Comirnaty (original) vaccine strain to the Omicron subvariant XBB.1.5 and to register new formulations.

To support this application, the sponsor has provided nonclinical study report, providing immunogenicity in mice. The quality data has been submitted for only two formulations out of the six proposed.

TGA has published a guidance for the Covid 19 vaccine strain update. This guidance aims to simplify the indication and dosing.[9]

Public health need

SARS-CoV-2 (Omicron variant) is still circulating in Australia.[10] There is a need for COVID-19 vaccine which provides better protection against the currently circulating Omicron subvariants.

Although Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccines provide some protection against a range of outcomes from XBB-related COVID-19,[11,12] evidence suggests that vaccines better matched to currently circulating strains can offer improved protection against symptomatic and severe disease.[13]

Proposed indication

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

[9] Therapeutic Goods Administration (TGA) COVID-19 Vaccine Strain Updates, last updated on 6 September 2023. Available at https://www.tga.gov.au/resources/resource/guidance/covid-19-vaccine-strain-updates.

[10] Department of Health and Aged Care, COVID-19 Reporting. Available at: https://www.health.gov.au/health-alerts/covid-19/weekly-reporting.

[11] Center for Disease Control and Prevention (CDC) Early Estimates of Bivalent mRNA Booster Dose Vaccine Effectiveness in Preventing Symptomatic SARS-CoV-2 Infection Attributable to Omicron BA.5 - and XBB/XBB.1.5-Related Sublineages Among Immunocompetent Adults - Increasing Community Access to Testing Program, United States, December 2022-January 2023, *MMWR*, 2023; 72(5): 119-124. Available at: http://dx.doi.org/10.15585/mmwr.mm7205e1.

[12] Center for Disease Control and Prevention (CDC) Estimates of Bivalent mRNA Vaccine Durability in Preventing COVID-19-Associated Hospitalization and Critical Illness Among Adults with and Without Immunocompromising Conditions - VISION Network, September 2022-April 2023, *MMWR*, 2023; 72(21): 579-588. Available at: http://dx.doi.org/10.15585/mmwr.mm7221a3.

[13] Khoury DS, et al. Predicting the Efficacy of Variant-Modified COVID-19 Vaccine Boosters, *Nature Medicine,* 2023; 29(3): 574-578. doi: 10.1038/s41591-023-02228-4.

Dosage and dose schedule

Table 7 lists the proposed dosage and dose schedule by sponsor for this application.

Table 7: Proposed dosage and dose schedule

Strength and Age of Individual	Volume of Each Dose	Dose Schedule for Primary Series and Booster
10 micrograms per dose 5 to <12 years	0.3 mL	**Primary series:** 2 doses at least to 21 days (preferably 3 weeks) apart
30 micrograms per dose 12 years and older	0.3 mL	**1st Booster**: at least 6 months after completion of primary series

Subsequent doses of Comirnaty Omicron XBB.1.5 may be administered to individual 18 years of age and older at least 3 months after a previous booster dose of Comirnaty.

The decision when and for whom to implement a booster dose of Comirnaty Omicron XBB.1.5 should be ased on available vaccine safety and effectiveness data (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties in Product Information), in accordance with official recommendations.

Immunogenicity

The Omicron XBB.1.5 containing variant vaccine as a primary series or booster dose was immunogenic in mice and induced significantly higher neutralising antibodies against Omicron XBB.1.5 and other related variants (XBB.1.16, XBB.1.16.1, XBB.2.3). The monovalent Omicron XBB.1.5 (0.5 µg) vaccine showed higher neutralising antibodies and T-cell response compared to the bivalent variant vaccine (Omicron BA.4/5 (0.25 µg) plus Omicron XBB.1.5(0.25 µg)).

Overall data limitation

There is no clinical efficacy or safety data and no available real world/post market data.

Proposed action

There is existing public health need for a COVID-19 vaccines to offer better protection against the currently circulating SARS-CoV-2 Omicron subvariants. This submission is for strain update, leveraging on the fully registered Comirnaty (original) vaccine. Based on the acceptable nonclinical immunogenicity data, and quality data, the Delegate is inclined to approve this variation. In addition to the submitted data with this application, the approval is also based on the full body of previous clinical, nonclinical, and real-world evidence supporting the safety and efficacy. There are issues raised in this overview, which will be discussed with the Advisory Committee on Vaccines (ACV) and a final decision will be taken only after that.

Proposed therapeutic indication and dosing

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

Table 8: Dosage

Strength and Age of Individual	Volume of Each Dose	Dose Schedule for Primary Series and Booster
10 micrograms per dose 5 to <12 years	0.3 mL	**Primary series:** 2 doses at least to 21 days (preferably 3 weeks) apart
30 micrograms per dose 12 years and older	0.3 mL	**1st Booster**: at least 6 months after completion of primary series

Subsequent doses of Comirnaty Omicron XBB.1.5 may be administered to individual 18 years of age and older at least 3 months after a previous booster dose of Comirnaty.

The decision when and for whom to implement a booster dose of Comirnaty Omicron XBB.1.5 should be made based on available vaccine safety and effectiveness data (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties in Product Information), in accordance with official recommendations.

Conclusion

This overview is submitted for the ACV advice. The ACV's advice is requested for the listed questions (see Advisory Committee considerations)

The final decision will be made following the ACV discussion and satisfactory resolutions of the subsequent PI issues.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please explain the discrepancy concerning the proposed dosing intervals. European Medicines Agency approved dosing interval states 'a dose at least 3 months after the primary vaccination or the booster dose'. A dosing interval of 'at least 6 months after primary immunisation and at least 3 months after the booster dose', is proposed in this application.***

The dosing intervals for a booster dose following completion of primary course for Comirnaty COVID-19 vaccines have evolved over the pandemic with everchanging disease landscape and emerging variants with antibody evading mutations. Comirnaty Original/Omicron BA.4-5 bivalent vaccine, which is the presentation latest approved, it is currently approved with the dosing interval of 'at least 3 month after…'.

The current approved dosing interval of six months after primary immunisation for the monovalent vaccine was approved in alignment with the dosing time point per the supporting clinical data available at the time in January 2022.

The sponsor takes this opportunity to indicate that Pfizer wishes to align the proposed PI to the EMA approved dosing interval and provides the rational for the 3-month booster interval, which is supported by immunogenicity data from Study C4591017, Study C4591001, and C4591031 Substudy D Cohort 1 and Cohort 2, safety data from Study C4591017, Study C4591001, and C4591031 Substudy D Cohort 1 as well as real-world evidence. Overview of the immunogenicity and safety data are presented below.

Overview of immunogenicity supporting 3-month interval

Study C4591017

Study C4591017 was comprised of a primary study and booster study. The primary study evaluated the safety, tolerability, and immunogenicity of 4 manufacturing lots of BNT162b2 as a

30 µg dose and an additional 20 µg dose arm. The booster study enrolled a subset of approximately 60 adult participants (18 to 50 years of age) who each received two 30 µg doses of BNT162b2 (Original) in the primary study. Participants were randomly assigned in a 1:1 ratio to receive either BNT162b2 or BNT162b2 (B.1.351) at 30 µg as a booster dose (BNT162b2 [B.1.351] contained the Beta variant-specific mutations of South African origin and is also referred to as BNT162b2SA, BNT162b2s01, or BNT162b2.B.1.351 and hereafter referred to as BNT162b2 [B.1.351]). In the booster study, the booster dose (Dose 3) was administered approximately three months after BNT162b2 Dose 2 of the primary study. In the booster evaluable immunogenicity population and for both vaccine groups (N = 53), geometric mean titres (GMTs) for the reference strain had decreased between 1MPD2 (one month post Dose 2) and just prior to the booster (Dose 3). After administration of the booster (Dose 3), GMTs in both the BNT162b2 and BNT162b2 [B.1.351] groups increased to greater than 1MPD2 levels.

Study C4591001

Study C4591001 included participants 18 to 55 years of age who received BNT162b2 [B.1.351] as booster doses (Dose 3 [N = 30] and Dose 4 [N = 28]) approximately one month apart, after 2 doses of BNT162b2 30 µg. Most participants in this group received the first booster (Dose 3) at least 6 months after Dose 2, and most received the second booster (Dose 4) between 28 and 34 days after Dose 3. Among BNT162b2-experienced participants in the Dose 3 booster evaluable immunogenicity population (N = 30) and Dose 4 booster evaluable immunogenicity population (N = 27) without prior evidence of SARS-CoV-2 infection up to one month after Dose 4, SARS-CoV-2 50% neutralising GMTs for the Beta variant and reference strain increased after administration of the first booster dose (Dose 3). GMTs for the Beta variant and reference strain further increased after the second booster dose (Dose 4) relative to 1 month after the first booster dose (Dose 3), further boosting the neutralising antibody response for both the Beta variant and reference strain.

Study C4591031 Substudy D Cohort 1 and Cohort 2

Study C4591031 Substudy D included the cohorts and groups presented below in Table 9.

Table 9: Study C4591031 Substudy D: Cohort 1 and Cohort 2

Cohort	Group	Prior BNT162b2 Experience	Study Vaccine	Number of Doses Administered
Cohort 1	Group 1	2 Doses	BNT162b2 (OMI BA.1)	1
	Group 2	2 Doses	BNT162b2 (OMI BA.1)	2 (1 Month Apart)
	Group 2b	2 Doses	BNT162b2 (original)	1
Cohort 2	Group 3	3 Doses	BNT162b2 (OMI BA.1)	2 (3 Month Apart)
	Group 4	3 Doses	BNT162b2 (Original) (Dose 4) And BNT162b2 (OMI BA.1) (Dose 5)	2 (3 Month Apart)

a Data presented in this cohort are from a subset of about 30 participants per group serving as sentinel groups for immunogenicity assessment. Participants in the subset will not contribute to the assessment of primary and secondary immunogenicity objectives. Immunogenicity data from these participants will be summarised separately for the exploratory objective specific for the subset.

b. Data presented in this cohort are from about 40 participants per group (subsets) selected from the entire cohort such that half are baseline positive and half are baseline negative. The second study intervention was BNT162b2 (Omicron BA.1) 30 µg for both vaccine groups.

Cohort 1 Sentinel Groups – Participants with or without evidence of infection, evaluable immunogenicity population:

- Group 1 (N = 29): Median time between Dose 2 of BNT162b2 (Original) and first booster dose (Dose 3) was 5.9 months (range: 3 to 8 months).

- Group 2 (N = 25): Median time between Dose 2 of BNT162b2 (Original) and first booster dose (Dose 3) was 5.5 months (range: 3 to 8 months).
- Group 2b (N = 28): Median time between Dose 2 of BNT162b2 (Original) and first booster dose (Dose 3) was 5.6 months (range: 3 to 7 months).

For all groups, GMTs for BA.1, the reference strain, and BA.4/BA.5 increased one month after administration of the first booster dose (Dose 3). For Group 2, GMTs for BA.1, the reference strain, and BA.4/BA.5 further increased one month after the second booster dose (Dose 4) relative to one month after the first booster dose (Dose 3), further boosting the neutralising antibody response for BA.1, the reference strain, and BA.4/BA.5.

Cohort 2 Subsets – Participants with or without evidence of infection, evaluable immunogenicity population:

- Group 3 (N = 40): Median time between Dose 3 of BNT162b2 (Original) and second booster dose (Dose 4) of BNT162b2 (Omicron BA.1) was 3.8 months (range: 3.2 to 6.4 months).
- Group 4 (N = 38): Median time between Dose 3 of BNT162b2 (Original) and second booster dose (Dose 4) of BNT162b2 (Original) was 4.0 months (range: 3.3 to 6.4 months).
- For Groups 3 and 4, Dose 5 of BNT162b2 (Omicron BA.1) was administered at the 3-month follow-up visit.

In both groups, GMTs for BA.1 and the reference strain increased after the second booster dose (Dose 4) but decreased 3 months after the second booster dose (Dose 4). After administration of the third booster (Dose 5), GMTs for both BA.1 strain in both groups increased to greater than 1MPD4 levels.

Overview of safety supporting 3-month interval

Study C4591017

In Study C4591017, a booster dose (Dose 3) of either BNT162b2 or BNT162b2 (B.1.351) at 30 μg was administered approximately three months after BNT162b2 Dose 2 of the primary study. 93.5% (58 of 62) of participants received the booster dose (Dose 3) 83 to 97 days after Dose 2. The most common reactogenicity events for the booster study included pain at the injection site, fatigue, headache, and new or worsened muscle pain. The proportion of participants in the booster study who reported pain at the injection site was higher after Dose 3 compared to after Dose 2, but similar for local reactions redness and swelling. In the booster study, similar proportions of participants reported systemic events after Dose 3 and Dose 2. Overall, the proportion of participants reporting AEs in the booster study was low across all vaccine groups (1 related event; no severe adverse event (AE), serious adverse events (SAE), or AEs leading to withdrawal).

Study C4591001

In Study C4591001, participants received BNT162b2 [B.1.351] as booster doses (Dose 3 and Dose 4) approximately 1 month apart after a primary series with BNT162b2 (N = 30; 22 to 55 years of age). Most participants in this group received the first booster (Dose 3) at least 6 months after Dose 2, and most received the second booster (Dose 4) between 28 and 34 days after Dose 3. Local reactions and systemic events were generally similar or lower in frequency after the second booster (Dose 4) compared with first booster (Dose 3). Local and systemic reactogenicity events were well-tolerated and short-lived. Most reactogenicity events were mild or moderate in severity, with no Grade 4 events. The frequency of participants with any AE from the first booster (Dose 3) to 1 month after the second booster (Dose 4) was 6 (20%), with one participant experiencing an unrelated SAE and two participants experiencing AEs leading to

withdrawal from study intervention. No additional participants reported AEs from Dose 3 to approximately five months after Dose 4.

Study C4591031 Substudy D Cohort 1

In Study C4591031 Substudy D Cohort 1, sentinel groups (30 participants each in Groups 1, 2, and 2b safety populations; total N = 90) received BNT162b2 (Omicron BA.1) or BNT162b2 (Original) as a booster dose (Dose 3), with participants in Group 2 additionally receiving a second booster dose (Dose 4) of BNT162b2 (Omicron BA.1) 1 month later. The most common reactogenicity events for participants in the Cohort 1 sentinel groups included pain at the injection site, fatigue, headache, and new or worsened muscle pain. In Group 2, except for swelling, headache, and muscle pain, local reactions and systemic events were generally similar or lower in frequency after the second booster (Dose 4) compared with first booster (Dose 3). Local and systemic reactogenicity events were well-tolerated and short-lived. Most reactogenicity events were mild or moderate in severity, with no Grade 4 events. Overall, the proportion of participants reporting AEs in the Cohort 1 sentinel groups was low across all vaccine groups. In Group 2, one participant experienced a related AE. In Group 3, one participant experienced an SAE (severe), and one participant experienced a related AE.

Conclusions

Together, the available clinical trial and real-world data (US CDC study and Israel population-based cohort study) have demonstrated use of a range of dosing intervals between primary vaccination and subsequent booster doses. An interval of at least 2 to 3 months between the last dose (primary or booster) and subsequent doses with Comirnaty and/or Comirnaty Original/Omicron BA.4-5 (Bivalent) has not revealed new or unexpected safety findings in individuals at least 6 months of age, while the benefit of vaccination in all age groups has remained favourable. The epidemiology of SARS-CoV-2, the effectiveness and safety of the vaccines will continue to be monitored by Pfizer and BioNTech.

2. Can the sponsor provide information whether there is a plan for post marketing clinical trial to assess efficacy/immunogenicity/safety for the Comirnaty XBB 1.5?

The sponsor confirms that there are post-marketing clinical trials planned/on-going to assess the safety, tolerability and immunogenicity for the proposed Comirnaty Omicron XBB.1.5 COVID-19 vaccine in healthy individuals. Please see below for the information requested.

Study Protocol C4591054

The monovalent XBB.1.5 vaccine will be evaluated in Study C4591054, a Phase II/III protocol to investigate the safety, tolerability, and immunogenicity of BNT162b2 RNA-based vaccine candidates for SARS-CoV-2 new variants in healthy individuals.

In Study C4591054 Substudy A (SSA), participants 12 through 55 and older than 55 years of age who have received at least three prior doses of a US-authorised mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5–adapted bivalent vaccine received at least 150 days prior to study vaccination, will receive a single open-label 30 µg dose of Pfizer/BioNTech COVID-19 2023-2024 formula (monovalent XBB.1.5 vaccine).

Approximately 400 participants were enrolled [Information redacted]. This substudy started in third quarter of 2023 [Information redacted]..

Study C4591054 Substudy B (SSB) is planned to demonstrate the noninferiority with respect to level of neutralising titre and seroresponse rate of the anti-XBB.1.5 immune response elicited by a single dose of the monovalent XBB.1.5 vaccine in approximately 300 COVID-19 vaccine-naïve participants at least 12 years of age who were previously SARS-CoV-2 exposed compared to a single dose of the monovalent XBB.1.5 vaccine given to vaccine-experienced participants in SSA.

Study Protocol C4591048

The monovalent XBB.1.5 vaccine will be evaluated in Study C4591048, protocol to investigate the safety, tolerability, and immunogenicity of variant-adapted BNT162b2 RNA-based vaccine candidates for SARS-CoV-2 new variants in healthy individuals in vaccine naïve children and vaccine experienced children 6 months to 11 years.

Advisory Committee considerations

The Advisory Committee on Vaccines (ACV), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Does the ACV support the proposed indication?

The ACV supported the proposed indication:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

The ACV acknowledged that the epidemiology of COVID-19 supports a need for a vaccine targeted to protect against the currently-circulating SARS-CoV-2 variant of concern, Omicron XBB.1.5 and related emerging sub-variants. The ACV noted that the main objective of an update to COVID-19 vaccine target variant is to achieve a wider breadth of immunity.

The ACV noted this submission is supported by quality data and that manufacture uses the same well-characterised mRNA platform as for earlier versions of Comirnaty COVID-19 vaccines. The ACV noted the submission was supported by preclinical (immunogenicity in mice) data but not clinical data. The ACV noted that the sponsor has commenced clinical studies for safety, tolerability and immunogenicity data in both vaccine-naive and previously-vaccinated human subjects.[14]

Overall, the ACV supported the Delegate's view in favour of registration.

The ACV noted the proposed indication is for use in individuals 5 years and older. The ACV noted that regulatory agencies in Europe and Canada have approved use for individuals from 6 months of age, and in the USA use in individuals from 6 months to <12 years of age is authorised (under Emergency Use Authorization) and approved (under a Biologics License Application) in individuals 12 years and older. The ACV highlighted the need for a vaccine for infants from 6 months of age and young children who are at risk of severe COVID-19 using a vaccine relevant to currently-circulating strains rather than against the original wild-type virus and advised availability of updated vaccines in this age group is a current gap in Australia.

2. Does the ACV agree with proposed dosing schedule for primary and booster doses?

The ACV agreed with the proposed dosing of 30 µg raxtozinameran for individuals 12 years and older, and 10 µg raxtozinameran for individuals aged 5 to <12 years.

The ACV advised that a simplified dosing schedule (compared with earlier Comirnaty vaccines) would be appropriate.

[14] See EMA statement published 30 May 2023. Global regulators agree on way forward to adapt COVID-19 vaccines to emerging variants | European Medicines Agency (europa.eu)

The ACV advised that information regarding how to administer a primary (that is, multi-dose) series, when clinically indicated, should be included in the dosage section of the PI and include details specific for use in such individuals, such as those who are vaccine -naive and immunocompromised individuals. Reference should be made to use of the vaccine in accordance with clinical recommendations in Australia, that is, as made by the ATAGI in the Australian Immunisation Handbook.

General reference to 'booster' doses in the product information is no longer useful or accurate. Raxtozinameran is a different active ingredient to the tozinameran used in the original Comirnaty vaccine, with nucleoside modified mRNA (modRNA) adapted to target Omicron XBB.1.5, and Comirnaty Omicron XBB.1.5 vaccine is not boosting the immune response against the wild-type virus (which is no longer circulating). The terms 'Subsequent' or 'Additional' dose(s) could be used instead of 'booster' where needed. The ACV advised that subsequent doses could be administered at least 3 months after the most recent COVID-19 vaccine, including to people under 18 years of age.

In providing this advice the ACV noted that the doses and dosing schedule are supported by immunogenicity and safety data and real-world experience with earlier Comirnaty vaccines. The simplified schedule aligns with that approved by the European Medicines Agency.

3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application?

The ACV noted that safety and immunogenicity has been inferred from extensive clinical studies and real-world experience with earlier Comirnaty vaccines. Given this, the following statement could be included in the PI:

'The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccines.'

The ACV supported the inclusion of additional information in the PI regarding pregnancy and breast-feeding, such as the following information from the European Summary of Product Characteristics:

'*No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.*

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.'

Conclusion

Overall, the ACV agreed with Delegate.

Outcome

Based on a review of quality, nonclinical and safety/efficacy data (inferred from original Comirnaty data), the TGA approved the registration of Comirnaty Omicron XBB.1.5

(raxtozinameran) 3 µg/0.3 mL, 3 µg/0.2 mL, 10 µg/0.3 mL, 10 µg/0.2 mL, and 30 µg/0.3 mL, suspension for injection, single dose vial and multidose vial, indicated for:

> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 6 months of age and older.*
>
> *The use of this vaccine should be in accordance with official recommendations.*

Specific conditions of registration applying to these goods

- Comirnaty Omicron XBB.1.5 (raxtozinameran) is to be included in the Black Triangle Scheme. The PI and CMI for Comirnaty Omicron XBB.1.5 must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the products.
- Batch release testing and compliance

  It is a condition of registration that all independent batches of

  - Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 30 µg/0.3 mL suspension for injection multi-dose vial [AUST R 419330]
  - Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 10 µg/0.3 mL suspension for injection single-dose vial [AUSTR R 419371]
  - Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 30 µg/0.3 mL suspension for injection vial [AUSTR R 419370]
  - Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 10 µg/0.2 mL concentrated suspension for injection multidose vial [AUSTR R 419331]
  - Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 10 µg/0.3 mL suspension for injection multidose vial [AUST R 419372]
  - Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 3 µg/0.2 mL concentrated suspension for injection multidose vial [AUSTR R 419332]
  - Comirnaty Omicron XBB.1.5 (raxtozinameran) COVID-19 vaccine 3 micrograms/0.3 mL concentrated suspension for injection multidose vial [AUSTR R 428610]

  vaccine imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and sponsor have received notification acknowledging release from the Laboratories Branch, TGA.

  For each independent batch of the product imported into Australia, the sponsor must supply the following:

  - A completed Request for Release Form, available from vaccines@health.gov.au.
  - Complete summary protocols for manufacture and QC, including all steps in production in the agreed format.
  - At least ten (10) vials (samples) of each manufacturing batch of the above listed vaccines with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted) representative of all batches of product seeking distribution in Australia.
  - At least five (5) vials (samples) of any further consignments of a manufacturing batch of the above listed vaccines with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted). Further consignments cover

batches previously supplied to TGA for the purposes of batch release testing but are seeking to be supplied again.

- If the manufacturing batch has been released in Europe or United Kingdom a copy of the EU Official Control Authority Batch Release (OCABR) certificate (or equivalent from the UK) must be provided.
- Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA

  Sponsors must provide all requested samples and data in sufficient time (at least 5 business days) prior to any distribution date to allow the TGA to perform testing and review. Distribution of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

  Samples and data should be forwarded to the Biotherapeutics Section, Laboratories Branch before release of each batch and with sufficient lead time to allow for Laboratories Branch testing.

  The shipments (including reagents) to TGA are the responsibility of the Australian sponsor/agent who will be required to facilitate the import and customs clearance process.

Certified Product Details

An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) https://www.tga.gov.au/guidance-7-certified-product-details should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescriptionmedicines]. The CPD should be sent as a single bookmarked PDF document to Vaccines@health.gov.au as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

- Post approval commitments
  - GMP [Good Manufacturing Practice] clearance for listed manufacturers: All relevant manufacturing sites require approved and current GMP clearances prior to Australian supply. A commitment is required from the sponsor that they maintain the validity of all manufacturer GMP clearances for the duration of product supply to Australia. Additionally, that adherence to the conditions of GMP Clearance approval is upheld.
  - Post-approval stability protocol and stability commitment: The manufacturer has provided commitment to continue the ongoing stability studies presented in the stability studies protocol. Additionally, one (1) batch of drug product per year for all relevant products will be placed on long-term stability program and on accelerated stability testing where significant changes are made to the manufacturing process. The manufacturer has committed to communicate any out of specifications stability test results to the TGA.
  - Batch Analysis (DS and DP): Provide batch analysis data for additional DS and DP batches manufactured at the commercial scale once they become available to support batch-to-batch consistency. Due date: First quarter of 2024 [Stage I decision on AUST R 419330 and 419371] and March 2024 [Stage II decision on AUST R 419331, 419332, 419370, 419372 and 428610].

- Stability (DS and DP): Provide the results from ongoing stability studies performed on Omicron XBB.1.5 DS lots when stored at -20±5°C and 5±3°C for each time point in accordance with the stability testing protocols to support the shelf-life of the DS. Provide the results from ongoing stability studies performed on XBB.1.5 variant DP lots when stored at -90°C to -60°C and 5±3°C for each time point in accordance with the stability testing protocols to support the shelf-life of the DP. Due date: First quarter of 2024 [Stage I decision on AUST R 419330 and 419371] and March 2024 [Stage II decision on AUST R 419331, 419332, 419370, 419372 and 428610].
- Multidose vials: Four (4) of the proposed Omicron XBB.1.5 DP presentations are multidose vials. At this stage in the pandemic, a move to single dose presentations is preferable. A period of 18 months is recommended to phase out the use of multidose vials [Stage II decision on AUST R 419331, 419332, 419370, 419372 and 428610].

Attachment 1. Product Information

The PI for Comirnaty Omicron XBB.1.5 approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #