Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tozinameran

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

January 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- 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 (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An 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.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse event
AESI	Adverse event of special interest
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
BMI	Body mass index
CDC	Centers for Disease Control and Prevention (United States of America)
CI	Confidence interval
CMI	Consumer Medicines Information
COVID-19	Coronavirus disease 2019
CPD	Certified Product Details
CSR	Complete study report
DMC	Data monitoring committee
DP	Drug product
DS	Drug substance
EU	European Union
EUA	Emergency Use Authorization (United States of America)
FDA	Food and Drug Administration (United States of America)
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
ICH	International Council for Harmonisation
OCABR	Official Control Authority Batch Release
PI	Product Information
PRM	Primary reference material(s)

Abbreviation	Meaning
PSURs	Periodic safety update reports
QC	Quality control
RNA	Ribonucleic acid
RVE	Relative vaccine efficacy
SAE	Serious adverse event
SAR-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGA	Therapeutic Goods Administration
USA	United States of America
WHO	World Health Organization
WRM	Working reference material(s)

I. Introduction to product submission

Submission details

Type of submission:	Major variation (change of dose regimen)
Product name:	Comirnaty
Active ingredient:	Tozinameran
Decision:	Approved for provisional registration
Date of decision:	27 January 2022
Date of entry onto ARTG:	28 January 2022
ARTG number:	377110
, *Black Triangle Scheme:*[1]	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Pfizer Australia Pty Ltd Level 17, 151 Clarence Street Sydney NSW 2000
Dose form:	Suspension for injection
Strength:	30 µg/0.3 mL
Container:	Multi-dose vial
Pack size:	195 vials
Approved therapeutic use:	*Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older.* *The use of this vaccine should be in accordance with official recommendations.* *The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.*
Route of administration:	Intramuscular

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Dosage:	*Individuals 12 years of age and older* Comirnaty is administered intramuscularly after dilution as a primary course of 2 doses at least 21 days apart. See dosing instructions below. A booster dose of Comirnaty may be administered intramuscularly at least 6 months after the completion of a COVID-19 vaccine primary series in individuals 16 years of age and older. The decision when and for whom to implement a booster dose of Comirnaty 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. There are limited data on the interchangeability of Comirnaty with other COVID-19 vaccines to complete the primary vaccination course or the booster dose. Individuals who have received one dose of Comirnaty should preferably receive a second dose of Comirnaty to complete the primary vaccination course and for any additional doses. *Severely immunocompromised aged 12 years and older* In accordance with official recommendations, a third dose may be given, as part of the primary series, at least 28 days after the second dose to individuals who are severely immunocompromised (see Section 4.4 Special warnings and precautions for use of the Product Information). *Elderly population* No dosage adjustment is required in elderly individuals ≥ 65 years of age. For further information regarding dosage, 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. This 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 application by Pfizer Australia Pty Ltd (the sponsor) to register Comirnaty (tozinameran) 30 µg/0.3 mL concentrated suspension for injection for the following changes to the dosage regimen:

Dosage update to include a booster dose:

> *A booster dose (third dose) of Comirnaty may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older.*

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a zoonotic virus that was first detected as a human pathogen in China and has rapidly spread around the world by human to human transmission.

In December 2019, a pneumonia outbreak of unknown cause was first described and in January 2020, it became clear that a novel coronavirus (named 2019-nCoV initially, later called SARS-CoV-2) was the underlying cause.[2] In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and the public, and the virus was categorised in the beta-coronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome coronavirus (also known as MERS).

SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterised the COVID-19 outbreak as a pandemic.[3] Since that announcement, the transmission of SARS-CoV-2 and resultant cases of COVID-19 disease has occurred globally, with cases reported by the vast majority of countries. As of 12 January 2022, there have been over 312 million globally confirmed COVID-19 cases and over 5.5 million deaths, with over 190 countries/regions affected.[4] In Australia, as of 12 January 2022, there have been over 1.1 million confirmed COVID-19 cases and 2465 deaths.[5]

The Omicron variant (B.1.1.529) of SARS-CoV-2 was designated by WHO as a variant of concern on 26 November 2021 and is currently circulating in many countries worldwide including Australia.[6]

The Pfizer-BioNTech COVID-19 vaccine, Comirnaty, is comprised of nucleoside-modified mRNA encoding a mutated form of the full length viral spike glycoprotein of SARS-CoV-2.[7] The ribonucleic acid (RNA) is encapsulated in lipid nanoparticles, which enables entry into host cells, expression of the spike glycoprotein, and elicitation of both antibody and cellular immune responses. The vaccine is supplied in a multidose clear glass 2 mL vial

[2] Zhu, N. et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019, *N. Engl. J. Med*, 2020; 382(8): 727-733.
[3] World Health Organization (WHO; 2020) WHO Director-General Speeches: WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 11 March 2020. Accessed 28 October 2021. Available from the WHO website.
[4] World Health Organization (WHO), Coronavirus Disease (COVID-19) Dashboard. Accessed 12 January 2022. Available from the WHO website.
[5] Australian Government, Department of Health (last updated 28 October 2021) Coronavirus (COVID-19) Case Numbers and Statistics. Accessed 12 January 2022.
Available at: https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-case-numbers-and-statistics.
[6] World Health Organization (WHO) media release on classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. Accessed 12 January 2022. Available at: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern
[7] Further information regarding mRNA technology in vaccines can be found at https://www.phgfoundation.org/documents/rna-vaccines-an-introduction-briefing-note.pdf.

with a rubber stopper, stored in -60 to -90°C. The vials are packed in cartons containing 195 multidose vials and are intended for use over a short time window (calculated from its first use) due to its preservative free composition.

Comirnaty (tozinameran), also known as the Pfizer/BioNTech COVID-19 vaccine was granted provisional registration;[8] on 25 January 2021 for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 16 years of age and older;[9]. The regimen is two doses, three weeks apart. Extension of indication to the age group of 12 to 15 years and older was approved on 21 July 2021.[10]Use in children 5 to 11 years and older was approved on 3 December 2021.[11] Change in dose regimen to include a booster dose in individual 18 years of age and older was approved on 26 October 2021.[12]

In this submission the sponsor was seeking approval to amend Section 4.2 Dose and method of administration of the PI regarding the update to the dose regime with a booster dose in individual 16 years of age and older in Australian Register of Therapeutic Goods (ARTG).[13]

Regulatory status

The product received initial registration (provisional) on the ARTG,[13] on 25 January 2021 for the prevention of COVID-19 in individuals 16 years of age and older. Subsequent applications have results in the approval for use in individuals 5 years of age and older.[11]

As of 13 January 2022, the approved indications for Comirnaty were:

> *Comirnaty (tozinameran) COVID-19 vaccine has provisional approval for the indication below:*
>
> *Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 5 years of age and older.*
>
> *A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the completion of a COVID-19 vaccine primary series in individuals 18 years of age and older.*
>
> *The decision when and for whom to implement a booster (third dose) of Comirnaty should be made based on available vaccine safety and effectiveness data (see Sections*

[8] As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.
The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available
[9] AusPAR for Comirnaty BNT162b2 (mRNA) Pfizer Australia Pty Ltd PM-2020-05461-1-2
available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna-comirnaty
[10] AusPAR for Comirnaty BNT162b2 (mRNA) Pfizer Australia Pty Ltd PM-2021-02187-1-2
available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna
[11] AusPAR for Comirnaty BNT162b2 (mRNA) Pfizer Australia Pty Ltd PM-2021-05012-1-2
available at: https://www.tga.gov.au/auspar/auspar-tozinameran-mrna-covid-19-vaccine
[12] AusPAR for Comirnaty BNT162b2 (mRNA) Pfizer Australia Pty Ltd PM-2021-04582-1-2
Available at: https://www.tga.gov.au/sites/default/files/auspar-bnt162b2-mrna-211029.pdf
[13] Therapeutic goods must be entered in the **Australian Register of Therapeutic Goods (ARTG)** before they can be lawfully supplied in or exported from Australia, unless exempt from being entered in the ARTG, or otherwise authorised by the TGA. For further information visit: https://www.tga.gov.au/australian-register-therapeutic-goods.

4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties), in accordance with official recommendations.

There are limited data on the interchangeability of Comirnaty with other COVID-19 vaccines to complete the primary vaccination course or the booster dose (third dose).

Individuals who have received 1 dose of Comirnaty should preferably receive a second dose of Comirnaty to complete the primary vaccination course and for any additional doses.

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

The decision has been made on the basis of short term efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

At the time the TGA considered this application, a similar application had been approved in the United States of America (USA) on 27 August 2021, European Union (EU) on 8 October 2021, United Kingdom on 9 September 2021, Canada on 1 October 2021 and New Zealand on 8 November 2021.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	27 August 2021	Approved: Emergency Use Authorization (EUA) on 22 September 2021 For 12 to 17 years old: EUA amended on 3 January 2022	*A single Pfizer-BioNTech COVID-19 Vaccine booster dose (0.3 mL) may be administered intramuscularly at least 6 months after completing the primary series to individuals:* • *65 years of age and older* • *18 through 64 years of age at high risk of severe COVID-19* • *18 through 64 years of age whose frequent institutional or occupational exposure to SARS CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19* The CDC updated its recommendations for the Pfizer and BioNTech COVID-19 vaccine booster to include children aged 12 to 17, citing rising infections in teens and young adults and an increase in pediatric hospitalisations. The authorisation includes recommendations for a booster dose at least five months after individuals received their second dose of the vaccine.
Canada	1 October 2021	Booster dose approved: 1 October 2021	*A booster dose may be administered at least 6 months after completion of the primary series in individuals 18 years of age or older.*

Region	Submission date	Status	Approved indications
European Union	2 September 2021	Booster dose approved 8 October 2021	*A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available vaccine effectiveness data, taking into account limited safety data.*
United Kingdom	20 August 2021	Approved temporary authorisation (Regulation 174) on 9 September 2021	*One dose of COVID-19 mRNA Vaccine BNT162b2 may be administered as a third dose at least 8 weeks after the second dose of an mRNA or adenovirus-vectored COVID-19 vaccine when the potential benefits outweigh any potential risks*
New Zealand	20 October 2021	Booster dose: Provisional consent 8 November 2021	*Extension of the dosing regimen to include use of a booster dose at least six months following completion of the primary course in individuals aged 18 years and older*

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, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application, and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2021-04582-1-2

Description	Date
Determination (Provisional);[8]	Not applicable
Submission dossier accepted and first round evaluation commenced	15 October 2021
Evaluation completed	5 January 2022
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 January 2022

Description	Date
Sponsor's pre-Advisory Committee response	10 January 2022
Advisory Committee meeting	14 January 2022
Registration decision (Outcome)	27 January 2022
Completion of administrative activities and registration on the ARTG	28 January 2022
Number of working days from submission dossier acceptance to registration decision*	68

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Efficacy

The clinical dossier consisted of the clinical study report for Study C4591031.

Study C4591031

Study design

Study C4591031 is a Phase III randomised, placebo controlled, observer blind substudy to evaluate the safety, tolerability, and efficacy of a booster dose of Comirnaty. Study participants ≥ 16 years of age from the pivotal Study C4591001 who completed a two dose of Comirnaty at least six months prior to randomisation were enrolled, and participants were randomised at a ratio of 1:1 to receive either Comirnaty or placebo. Randomisation was stratified by age, such that approximately 60% of participants enrolled would be ≥ 16 to 55 years of age and approximately 40% of participants > 55 years of age. Approximately 10000 participants were to be randomised.

The sponsor has provided the interim complete study report (CSR) version 1 (dated 18 November 2021) to Therapeutic Goods Administration (TGA). This study was conducted 123 sites in Brazil (2 sites), South Africa (4 sites), and the USA (117 sites). The analyses presented are based on a study initiation of 1 July 2021 (first participant first visit) and a database cutoff date of 5 October 2021.

The study was designed with interim efficacy analyses carried out after all participants reached two months of blinded follow up and every two months afterwards; and efficacy and safety analyses would be conducted when all participants complete blinded follow up (approximately 175 days after vaccination) and at the end of the study.

Planned data monitoring committee (DMC) review for the protocol pre-specified interim analysis of efficacy was conducted when all participants reached the two-month timepoint post booster, and the DMC recommended to unblind the study and continue unblinding of participants to allow placebo recipients the opportunity to receive a Comirnaty booster dose.

Participant randomisation

In total, 10,136 participants were randomised, including 5088 participants to receive a booster dose of Comirnaty (30 µg and 5048 participants were randomised to placebo(normal saline). Most randomised participants received a booster vaccination (99.9%) and most completed the one-month telephone contact during the blinded follow up period (99.1%).

Demographic characteristics

Demographic characteristics for all participants in the safety population were similar in the Comirnaty and placebo group. Overall, most participants were White (79%), with 9.2% Black or African American participants, 5.5% Asian participants, 4% Multiracial participants, and other racial groups comprising < 2%. There were 14.9% Hispanic/Latino participants. The median age at the time of study vaccination was 53 years, and 49.1% of participants were male. Most study participants (85.9%) were enrolled in the United States of America (USA).

545 participants (5.4%) had baseline positive status for evidence of prior infection with SARS-CoV-2, which was balanced across the Comirnaty and placebo groups. Baseline comorbidities were reported by 2390 participants (23.6%) and were balanced across Comirnaty and placebo groups.

The younger age group (16 to 55 years of age) made up 55.5% of the safety population; this included 90 participants (0.9%) who were 16 to 17 years of age. The older age group (> 55 years of age) made up 44.5% of the safety population; this included 2363 participants (23.3%) who were ≥ 65 years of age.

Results

Efficacy was assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19, which included confirmed COVID-19 cases and confirmed severe COVID-19 cases as defined by the Food and Drug Administration (FDA) USA and Centers for Disease Control and Prevention (CDC) USA.[14] The primary estimand defined for this substudy was relative vaccine efficacy (RVE) of the Comirnaty booster group to the non-booster group (placebo); it was estimated in participants without prior evidence of SARS-CoV-2 infection before or during the vaccine or booster vaccine regimen, and those with or without prior evidence of SARS-CoV-2 infection. All participants had previously received the primary series of Comirnaty 30 µg, therefore RVE compares a third dose of active vaccine versus placebo. Subgroup analyses of RVE were conducted based on demographics (age group, sex, race, and ethnicity), country, dose interval between second dose and booster dose, baseline SARS-CoV-2 status, and risk

[14] The definitions employed to categorise mild, moderate and severe COVID-19 disease were based on those proposed by the US FDA in their 'COVID-19: developing drugs and biological produces for treatment or prevention: guidance for industry'. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention

status based on Charlson Comorbidity Index;[15] or a body mass index (BMI) ≥ 30 kg/m^2. As all objectives were descriptive (counts, percentages, and the associated Clopper-Pearson two sided 95% confidence intervals (CI)), no hypothesis testing was applied.

For participants without evidence of infection prior to seven days after booster vaccination in the evaluable efficacy population, the median duration of blinded follow up after booster vaccination was 2.5 months as of the data cutoff date. Most participants (97%) had ≥ 2 to < 4 months of follow up time after booster vaccination.

The median follow up time was similar to the safety population for this population and also for the evaluable efficacy population participants with or without evidence of infection prior to seven days after booster vaccination.

Among participants without evidence of infection prior to seven days after booster vaccination in the evaluable efficacy population, based on the first COVID-19 occurrence from ≥ 7 days after booster vaccination to < 2 months after booster vaccination, the RVE was estimated as 95.6% (two sided 95% CI: 89.3%, 98.6%), based on five cases in the Comirnaty group and 109 cases in the placebo group.

Among participants with or without evidence of infection prior to seven days after booster vaccination in the evaluable efficacy population, based on the first COVID-19 occurrence from ≥ 7 days after booster vaccination to < 2 months after booster vaccination, the estimated RVE was 94.7% (two sided 95% CI: 88.2%, 98.1%), based on six cases in the Comirnaty group and 110 cases in the placebo group.

The RVE following booster vaccination was estimated from seven days post booster to the data cutoff date (5 October 2021) during the blinded placebo controlled follow up period. Cases in this RVE analyses accrued during a period of July to the October cutoff date, during a time that the highly transmissible Delta (B.1.617.2) variant has been the predominant SARS-CoV-2 strain in circulation in the USA and globally.

The RVE in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to seven days post-booster was observed as 95.3% (two sided 95% CI: 89.5%, 98.3%), based on six cases in the Comirnaty group and 123 cases in the placebo group (Table 3).

Table 3: Study C4591031 Vaccine efficacy, first COVID-19 occurrence from seven days after booster vaccination, blinded follow up period, participant without evidence of infection prior to seven days after booster vaccination (evaluable efficacy population)

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=4695)		Placebo (N[a]=4671)			
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after booster vaccination	6	0.823 (4659)	123	0.792 (4614)	95.3	(89.5, 98.3)

Abbreviation: BNT162b2 = Comirnaty; N-binding= SAR-CoV-2 nucleoprotein binding; NAAT = nucleic acid amplification test; RVE = relative vaccine efficacy of Comirnaty booster group relative to the placebo group (non booster); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (that is N-binding antibody (serum) negative at Visit 1

[15] Charlson Comorbidity Index is a weighted index to predict risk of death within 1 year of hospitalisation for patients with specific comorbid conditions. Nineteen conditions were included in the index. Each condition was assigned a weight from 1 to 6, based on the estimated 1 year mortality hazard ratio from a Cox proportional hazards model. These weights were summed to produce the Charlson comorbidity score.

and SARS-CoV-2 not detected by NAAT (nasal swab) at Visit 1, and had a negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis

[a] N = numberof participants in the specified group

[b] n1 = Number of participants meeting the endpoint definition

[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.

[d] n2 = Number of participants at risk for the endpoint

[e] two sided CI for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.

The RVE in the all-available efficacy (mITT) population from booster vaccination onwards was 89.8% (two sided 95% CI: 82.6%, 94.4%), based on 15 cases in the Comirnaty group and 141 cases in the placebo group reported after booster vaccination (Table 4).

Table 4: Study C4591031 Vaccine efficacy, first COVID-19 occurrence after booster vaccination, blinded follow up period (all available efficacy population)

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=5056)		Placebo (N[a]=5019)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
First COVID-19 occurrence after booster vaccination	15	0.978 (5003)	141	0.940 (4943)	89.8	(82.6, 94.4)
Booster vaccination to 7 days after booster vaccination	8	0.096 (5003)	15	0.095 (4943)	47.3	(-32.3, 80.7)
≥7 Days after booster vaccination to <2 months after booster vaccination	6	0.668 (4995)	112	0.645 (4928)	94.8	(88.4, 98.1)
≥2 Months after booster vaccination to <4 months after booster vaccination	1	0.214 (4891)	14	0.200 (4616)	93.3	(56.1, 99.8)

Abbreviation: BNT1622b = Comirnaty; RVE = relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non booster).

[a] N = number of participants in specified group

[b] n1 = number of participants meeting the endpoint function

[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from the booster vaccination to the end of the surveillance period for the overall row and from the start to the end of the range stated for each time interval.

[d] n2 = Number of participants at risk for the endpoint.

[e] Two sided CI for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.

As of the data cutoff date, two cases were reported in the all available efficacy population that met severe criteria per the FDA definition,[14] both in the placebo group. Both cases met the severe criterion of '*clinical signs at rest indicative of severe systemic illness*' (oxygen saturation as measured by pulse oximetry) an occurred in participants who were baseline SARS-CoV-2 negative (Table 5).

Table 5: Study C4591031 Vaccine Efficacy, first severe COVID-19 occurrence (based on FDA definition)[14] after booster vaccination, blinded follow up period (all available efficacy population)

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=5056)		Placebo (N[a]=5019)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	RVE (%)	(95% CI[e])
First severe COVID-19 occurrence (based on FDA definition) after booster vaccination	0	0.980 (5003)	2	0.956 (4943)	100.0	(-419.5, 100.0)
Booster vaccination to 7 days after booster vaccination	0	0.096 (5003)	0	0.095 (4943)	NE	
≥7 days after booster vaccination	0	0.884 (5003)	2	0.862 (4943)	100.0	(-418.8, 100.0)

Abbreviation: BNT1622b = Comirnaty; NE = not estimable; RVE = relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non booster).

[a] N = number of participants in specified group

[b] n1 = number of participants meeting the endpoint function

[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from the booster vaccination to the end of the surveillance period for the overall row and from the start to the end of the range stated for each time interval.

[d] n2 = Number of participants at risk for the endpoint.

[e] Two sided CI for RVE is derived based on the Clopper and Pearson method adjusted for surveillance time.

All ages analysed showed similarly high observed RVE; all were estimated to be > 90%. In the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to seven days post booster for the 16 to 17 years of age subgroup, 0 cases were reported in the Comirnaty group (n = 41) and 2 cases in the placebo group (n = 37) for RVE 100% but with wide 95% CI (-348.6, 100).

Safety

The safety population included a total of 10,125 participants: 5081 in the Comirnaty group and 5044 in the placebo group. From booster vaccination to the data cutoff date, which represents up to at least two months post booster follow up, a greater proportion of participants in the Cominaty group (25.2%) reported any adverse events (AE) compared with the placebo group (6.8%). This was driven primarily by any AEs considered by the investigator as related to study intervention, reported by 23.4% of participants in the Comirnaty group and 4.2% of participants in the placebo group. Any severe or serious AEs were reported across the Comirnaty and placebo groups by ≤ 0.8% and ≤ 0.5%, respectively.

The AE profile after booster vaccination reflected mostly reactogenicity events and did not suggest any clinically important short-term safety concerns for Comirnaty booster vaccination. Subgroup analyses did not suggest any specific safety concerns with regard to age, sex, race, ethnicity, country, baseline SARS-CoV-2 status, or human immunodeficiency virus positive status. There were few AEs of clinical interest corresponding to the CDC list of adverse events of special interest (AESI) reported in the booster safety population. Both lymphadenopathy (2.7% versus 0%) and rash (0.1% versus 0%) were more frequently reported after a booster dose of Comirnaty as compared with placebo, and both of these events are known to be adverse reactions of Comirnaty. No cases of vaccine associated anaphylaxis, hypersensitivity, myocarditis/pericarditis, or Bell's palsy were reported in Comirnaty recipients up to the data cutoff date.

One participant in the placebo group died due to an unrelated serious adverse event (SAE) of pulmonary embolism which occurred 52 days after receipt of booster vaccination (placebo).

One participant in the placebo group withdrew due to life threatening SAE of metastatic cancer.

Overall, the safety results following at least two months of follow up post booster in the Comirnaty and placebo booster groups showed no new safety concerns associated with booster dosing.

Post-marketing experience

Data was extracted for the period from July 30 to October 10, 2021, from the Israel Ministry of Health database regarding 4,696,865 persons aged 16 years or older who had received two doses of Comirnaty at least five months earlier.

Five age groups were analysed including a 16 to 29 years group. Across the age groups studied, rates of confirmed Covid-19 and severe illness were substantially lower among participants who received a booster dose of the Comirnaty vaccine than among those who did not.[16]

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[17]

Risk-benefit analysis

Delegate's considerations

The sponsor has submitted immunogenicity and safety data of a third dose of Comirnaty (30 µg) given to a subset of USA participants in Phase III Study C4591001 who previously received two doses of Comirnaty (30 µg). This group is comprised of 306 adults 18 to 55 years of age who received a third dose of Comirnaty (30 µg) approximately 6 (range: 4.8 to 8) months after receipt of second dose, with safety and immune response evaluations at one month after third dose.

There were no data on individuals aged < 18 years in the initial submission. The sponsor's report states '*the use of a booster dose in individuals 16 and 17 years of age is based on extrapolation of the safety and effectiveness demonstrated at least 18 to 55 years of age.*'

The Delegate and clinical evaluator noted immune responses at one month after third dose were compared to immune responses one month after second dose. The Delegate and clinical evaluator considered the interim data initially submitted has shown that a third dose of Comirnaty given six months after the primary vaccination series restored waning neutralising antibody titres against wild type SARS-CoV-2 to significantly higher levels than seen following the primary vaccination course. The benefit risk profile of a third dose of Comirnaty in individuals aged 18 years and older appears positive, provided its implementation is guided by vaccine effectiveness data and considering limited safety data.

[16] Bar-On YM, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. (2021) *N Engl J Med*; 385:2421-30.
[17] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

An interim CSR version 1 (dated 18 November 2021) has recently become available for Study C459103. This report concludes relative efficacy in the boosted group showed that Comirnaty at 30 μg given ≥ 6 months after the primary two dose series provided strong protection against COVID-19 in participants 16 years of age and older. This was shown in participants irrespective of evidence of prior infection with SARS-CoV-2 and across various demographic subgroups.

All ages analysed showed similarly high observed RVE; all were estimated to be > 90%. In the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to seven days post booster for the 16 to 17 years of age subgroup, zero cases were reported in the Comirnaty group (n = 41) and two cases in the placebo group (n = 37) for RVE 100% but with wide 95% CI (-348.6, 100). Severe cases were rare and only observed in the placebo group.

The tolerability and safety profile of Comirnaty 30 μg in participants ≥ 16 years of age at up to two months after booster vaccination (to the data cutoff date) was acceptable and consistent with results previously reported.

Proposed action

The Delegate considers the additional data available from the interim BioNTech/Pfizer CSR for Study C459103 provides adequate support a Dose and method of administration statement:

> '*A booster dose (third dose) of Comirnaty may be administered intramuscularly approximately 6 months after the second dose in individuals 16 years of age and older*'.

Advisory Committee considerations[18]

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 ACV agree that a booster dose (third dose) of Comirnaty may be administered in individuals 16 years of age and older?

The ACV advised that there is sufficient evidence to support changes to the Product Information to include a booster dose (third dose) of Comirnaty for individuals 16 years of age and older given ≥ 6 months after the primary 2-dose series. Protection against COVID-19 in participants ≥ 16 years was shown irrespective of evidence of prior infection with SARS-CoV-2 and across various demographic subgroups.

[18] The **Advisory Committee on Vaccines** (ACV) provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of vaccines supplied in Australia including issues relating to pre-market assessment, post-market monitoring and safe use in national immunisation programs.
The Committee is established under Regulation 39F of the Therapeutic Goods Regulations 1990 and the members are appointed by the Minister for Health.
The ACV was established in January 2017, following consolidation of previous functions of the Advisory Committee on the Safety of Vaccines (ACSOV) and the pre-market functions for vaccines of the Advisory Committee on Prescription Medicines (ACPM).
Membership comprises professionals with expertise in specific scientific, medical or clinical fields, or consumer health issues.

The ACV were reassured that there were no significant differences between the 16 to 17 years age group and the 18+ years age group in the immunogenicity, reactogenicity or effectiveness of Comirnaty.

The ACV was of the view that the safety data, although with limited numbers, showed the Comirnaty booster was well tolerated, with similar frequencies and intensities of reactogenicity as experienced after the second dose of the primary series.

The ACV noted that immunogenicity associated with a third dose against the Omicron (B.1.1.529) variant of interest was not available.

2. Does ACV consider the time of the booster dose might be shortened to 5 months in light of the recent NEJM publication?

The ACV considered that the time interval from primary series to booster dose could be shortened to 5 months when warranted. However, the safety and efficacy of a time interval shorter than 5 months is not clear.

The ACV discussed the potential risk of myocarditis, particularly within the 16 to 17 years old age group, who appear to be at the highest risk of myocarditis. The ACV was reassured by early data indicating that the rate of myocarditis appears lower after booster (third dose) compared to after the second dose. There continues to be a need to communicate the risk of myocarditis to vaccine recipients.

3. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to this supplementary decision.

The ACV noted that there is likely to be a minimum safe window between the second dose and the booster dose, but this is as yet undefined. The PI should include a statement such as:

> 'Data support an interval of 5 months. Safety for shorter intervals has not been established.'

The ACV noted Buchan et al,[19] in a preprint paper, suggests that the reporting rates of myocarditis/pericarditis were higher when the interval between first and second doses was shorter (that is ≤ 30 days). This supported the view that the interval between doses is an important safety consideration.

The ACV advised that wording in the PI should clearly differentiate third dose as a booster dose from the three dose primary series for persons 12 years and over who are immunocompromised.

The ACV supported alignment of terminology used within dosage directions (e.g. the use of 'booster dose' or 'third dose') across all COVID-19 vaccines.

The use and timing of Comirnaty booster in 16 to17 years old should be in accordance with official recommendations.

Conclusion

The ACV recommended the approval of changes to the Product Information of Comirnaty to include a booster (third) dose for persons 16 years and older.

The use and timing of Comirnaty booster in 16 to 17 years old should be in accordance with official recommendations.

[19] Buchan, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. Pre-print. *medRxiv*; posted 5 December 2021.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Comirnaty (tozinameran) 30 µg/0.3 mL, suspension for injection, multi-dose vial, change in dose regimen to:

> ***'Individuals 12 years of age and older***
>
> *Comirnaty is administered intramuscularly after dilution as a primary course of 2 doses at least 21 days apart. See dosing instructions below.*
>
> *A booster dose of Comirnaty may be administered intramuscularly at least 6 months after the completion of a COVID-19 vaccine primary series in individuals 16 years of age and older.*
>
> *The decision when and for whom to implement a booster dose of Comirnaty 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 accordance with official recommendations.*
>
> *There are limited data on the interchangeability of Comirnaty with other COVID-19 vaccines to complete the primary vaccination course or the booster dose. Individuals who have received 1 dose of Comirnaty should preferably receive a second dose of Comirnaty to complete the primary vaccination course and for any additional doses.*
>
> ***Severely immunocompromised aged 12 years and older***
>
> *In accordance with official recommendations, a third dose may be given, as part of the primary series, at least 28 days after the second dose to individuals who are severely immunocompromised (see Section 4.4 Special warnings and precautions for use).*
>
> ***Elderly population***
>
> *No dosage adjustment is required in elderly individuals ≥ 65 years of age.'*

Specific conditions of registration applying to these goods

- Comirnaty vaccine is to be included in the Black Triangle Scheme due to provisional approval. The PI and CMI [Consumer Medicines Information] for Comirnaty vaccine must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.
- [Risk management plan]

  The Comirnaty EU-risk management plan (RMP) (version 2.2, dated 15 July 2021, data lock point 13 March 2021 (Pfizer clinical database), 28 February 2021 (Pfizer safety database - 12 to15 [years]), 23 October 2020 (BioNTech clinical database - ≥ 16 [years]), 28 February 2021 (Pfizer safety database and post-authorisation exposure)), with Australian specific annex (version 0.3, dated 11 June 2021), included with Submission, PM-2021-04582-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of

the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Additional to the routine submission of the routine PSURs, expedited monthly, Comirnaty safety summary reports (including safety data for patients in Australia) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

- Clinical

  Data relating to booster dose

  – Submit the clinical study report of NCT04955626 study to evaluate the safety and efficacy of a booster dose of BNT162b2 against COVID-19 in participants ≥ 16 years of age.

- Data relating to individuals 12 to 15 years old

  – Submit safety data for all adolescents 12 to 15 years of age in Study C4591001, 6 months post Dose 2, when the data becomes available.

  – Submit study report of Study C4591001, including data up to 24 months after Dose 2 in adolescents 12 to 15 years of age, when the data becomes available.

  Data relating to individuals 16 years and older

  – Submit safety data in relation to follow-up at 6 months post-Dose 2 for all original Comirnaty recipients and at 6 months post-Dose 4 for original placebo recipients subsequently vaccinated with Comirnaty ([that is], 6 months following their second dose), when the analysis is available.

  – Submit final completed study report for Study C4591001, including data up to 24 months after Dose 2 for individuals 16 years and older, when the data becomes available.

  – Submit final study reports for Study BNT162-01 once completed, including data on healthy subjects.

  When available, further data relating to vaccine efficacy against asymptomatic disease, vaccine efficacy in immunocompromised subjects, paediatric subjects, pregnant women, lactating mothers, and the information relating to post-market safety and effectiveness studies should be provided to the TGA, as separate submissions, to update the Product Information.

- Quality

  Medicine labels

  – The medicines must not be supplied with labels other than the labels that have been determined to be acceptable as part of the provisional registration of the Medicines under section 25, or, as relevant, any amended/additional labels subsequently approved under section 9D of the Act.

  – The sponsor will develop Australian-specific labels for the products, that conform with all relevant Australian labelling requirements, and will take all reasonable steps to implement such labelling before the end of the provisional registration

period referred to in subsection 29(3) of the Act (being the period of 2 years starting on the day specified in the ARTG certificate of registration) (noting that, consistent with paragraph 28(5) (aaa) of the Act, changes to such matters as labels that have been agreed to as part of an evaluation under section 25 of the Act may only occur following submission under section 9D of a 'variation' application and approval by the TGA).

  - The sponsor will provide information to the TGA on the proposed strategies and planned timelines for Australian dedicated supplies, as soon as possible, and no later than 24 January 2023.

- Batch release testing and compliance

  It is a condition of registration that all independent manufacturing batches of Comirnaty (BNT162b2 (mRNA)) COVID-19 vaccine to be supplied in Australia are not released for supply by or on behalf of the sponsor until samples and the manufacturer's release data have been assessed by, and you have received notification acknowledging authorisation to release from, the Laboratories Branch, TGA.

  In complying with the above, the sponsor must supply the following for each independent batch of the products imported or proposed to be imported into Australia:

  - a completed request for release form, available from vaccines@health.gov.au; and
  - complete summary protocols for manufacture and QC [quality control], including all steps in production in the agreed format; and
  - 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 also be provided; and
  - any reagents, reference material and standards required to undertake testing as requested by Laboratories Branch, TGA.

  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-biologicalprescriptionmedicines.

  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

  Section 3.2.S.2.1 and 3.2.P.3.1 Manufacturers/Section 3.2.A.1

  The sponsor has submitted the list of manufacturing sites along with the responsibilities in the production of the Comirnaty (BNT162b2 (mRNA) COVID-19 vaccine drug substance (DS) and drug product (DP) and specified functions.

The sponsor must maintain the validity of all manufacturer GMP [Good Manufacturing Practice] clearances for the duration of product supply to Australia and comply with any conditions of GMP clearance.

Section 3.2.S.5 Reference standards or materials

The sponsor must:

- Supply the data for the PRM [primary reference materials] and WRM [working reference materials] once generated and the certificates of analysis of reference standards made available upon request.
- Submit additional stability data (for a duration of 1 to 6 months and 12 to 60 months) for reference standards and materials as soon as it becomes available.
- Provide a protocol for the establishment of replacement reference standards (WRMs) including acceptance criteria and verification data.
- Notify the TGA of any change to the source of the lipid reference materials.

Section 3.2.S.7.2 Post-approval stability protocol

Upon completion of the ICH [International Council for Harmonisation] stability protocols, a minimum of 1 batch of BNT162b2 DS manufactured will be rolled in the commercial stability program at the long term storage conditions of -20 ± 5°C for each year that DS is manufactured. Additionally, a minimum of one batch will be placed in the commercial stability program at the long term storage condition of -90 to -60°C each year of DP manufacture.

Additional stability data (long term, accelerated and thermal stress study data for a duration of ≥ 6 months for a minimum of 2 to 3 clinical or commercial batches) must be submitted to the TGA as it becomes available. Once additional data have been submitted to the TGA for evaluation, an extended shelf life and/or change in storage conditions for the DS and/or DP may be considered.

Data and updated protocols for the currently ongoing thermal cycling studies must be submitted once available.

Any out of specification stability results for DS and/or DP should be submitted to the TGA as soon as they are generated.

The sponsor must inform the TGA of any temperature deviation during shipment and not supply product that has been exposed to a temperature excursion outside of the approved storage conditions of -90°C to -60°C.

Section 3.2.S.4.3 and 3.2.P.5.4 Batch analysis

The sponsor must provide to the TGA:

- a quality risk assessment or investigation report to explain the reason for the deviation in trend ([approximately] 10 fold increase increase) observed for the final 3 batches of commercial scale material manufactured at Pfizer, Andover (20Y513C501 20Y513C601 20Y513C701). Any remediation work that may have been implemented should be outlined.

Commercial scale batches

The sponsor must:

- Perform testing of future process-validation batches of the commercial scale finished product according to the comparability testing protocol/plan and provide results for assessment by the TGA when available.

Attachment 1. Product Information

The PI for Comirnaty approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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