Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Vaccines Meeting 32 Minutes on Item 2.1 Tozinameran (formerly BNT162b2 [mRNA])

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

22 March 2022

TGA Health Safety Regulation

Contents

Submission details

Type of submission:	Major variation / PI change requiring evaluation – changes in population for booster dose
Product name:	Comirnaty
Active ingredient:	Tozinameran (formerly BNT162b2 [mRNA])
Submission:	PM-2022-00483-1-2
Dose form:	Concentrated suspension for injection, and tris/sucrose suspension for injection
Strength:	30 microgram per 0.3 mL dose, embedded in lipid nanoparticles
Approved indication:	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. 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.
Approved dosage:	*Booster dose* 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.
Dosage proposed by sponsor:	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 12 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.

Documents considered by ACV

The ACV considered the following documentation, provided between 10 and 16 March 2022:

A1 Delegate - Request for ACV advice and overview, inclusive of clinical review – 'Delegate's Overview' – dated 10 March 2022
A2 Sponsor - application letter - dated 22 February 2022

A3 Sponsor – pre-ACV response
- A3 response
- A3a adverse reactions update
- A3b comments on PI
- A3c foreign regulatory status
- A3d comments on foreign PI

A4a ACV – ACV 22 ratified minute on primary dose in 12-15 year olds
A4b ACV – ACV 26 ratified minute on booster dose in 18+ year olds
PI Product Information – clean and annotated – from pre-ACV response
PI Product Information – clean and annotated – Tris/sucrose formulation - from pre-ACV response
CMI Consumer Medicine Information – clean and annotated – from pre-ACV response
CMI Consumer Medicine Information – Tris/sucrose formulation - clean and annotated – from pre-ACV response
EMA European summary of product characteristics – from pre-ACV response
UK UK information for temporary supply authorisation – dated 2 December 2021 - from pre-ACV response
CAN Canadian product monograph – dated 4 March 2022 - from pre-ACV response
USA USA fact sheet for vaccination providers – grey vial – dated 31 January 2022 - from pre-ACV response
USA USA fact sheet for vaccination providers – purple vial – dated 31 January 2022 - from pre-ACV response

Public materials discussed at the meeting included:

Hause AM, Baggs J, Marquez P, et al. Safety Monitoring of COVID-19 Vaccine Booster Doses Among Persons Aged 12–17 Years — United States, December 9, 2021–February 20, 2022. MMWR Morb Mortal Wkly Rep 2022;71:347–351. DOI: http://dx.doi.org/10.15585/mmwr.mm7109e2

Oster ME, Shay DK, Su JR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA. 2022 Jan 25;327(4):331-340. doi:10.1001/jama.2021.24110

Preprints:

Powell AA, Kirsebom F, Stowe J, et al. Adolescent vaccine effectiveness with BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine and effectiveness against COVID-19: national test-negative case-control study, England. medRxiv preprint, Feb 2022. doi: https://doi.org/10.1101/2021.12.10.21267408

Dorabawila V, Hoefer D, Bauer UE, et al. Effectiveness of the BNT162b2 vaccine among children 5-11 and 12-17 years in New York after the Emergence of the Omicron Variant. medRxiv preprint, Feb 2022. https://doi.org/10.1101/2022.02.25.22271454

Delegate's Overview

Delegate's summary of issues

This booster recommendation is based on extrapolation of effectiveness data in adults 16 to 55 years of age to the younger cohort of adolescent 12 to 15 years of age.

Safety is supported by real world surveillance of adverse events from Israel and USA. The exposure reported from Israel is insufficient for assessment of risk of myocarditis.

The Delegate recommends some product information changes are appropriate under Section 4.4 Special Warnings, Paediatric use.

Summary of data

The lower age of booster was supported by a Module 2.5 Clinical Overview based on:

- Safety data from the Israel Ministry of Health showing that after administering a single booster dose to more than 6,000 12- to 15-year-olds, no new safety concerns were identified through 15 December 2021
- Published data in adults showing that a single booster dose can greatly improve effectiveness against a range of SARS-CoV-2 outcomes compared to after only two doses administered at least five months ago
- Emerging evidence suggesting that three doses of vaccine may be especially necessary for preventing omicron related disease.

Other PI changes are supported by a Module 2.5 clinical overview and Module 5.3.5.1 C4591001 Interim clinical study report 6 months post-dose 2 in adolescents.

Delegate's preliminary view

The Delegate is proposing to approve the registration of the product Comirnaty with a statement a booster dose of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 12 years of age and older.

Advice sought by Delegate of the Secretary of the Department of Health

1. Does ACV agree that a booster dose of Comirnaty may be administered in individuals 12 years of age and older, based on extrapolation from data in adults 18 to 55 years of age?
2. Does ACV agree with the product information changes proposed by the sponsor?
3. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to this decision.

ACV discussion

Environment

The ACV noted that the vaccine was provisionally registered on the ARTG on 25 January 2021 for use in persons from 16 years of age. Continued approval is dependent on evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment. (See ACV 18, held 15 January 2021, providing advice on new biological entity).

Supply of the vaccine commenced on 21 February 2021.

The ACV also noted the provisional registration on 22 July 2021 for use in persons from 12 years of age. (See ACV 22, held 16 June 2021, providing advice on extension of indication).

The ACV also noted the dosage and PI changes approved 26 October 2021 for use of third doses. (See ACV 26, held 25 October 2021, providing advice on booster dose for 18+ years and third primary dose in immunocompromised persons 12 years and older).

The ACV also noted the dosage and PI changes approved 27 January 2022 for use of booster doses in persons from 16 years of age. (See ACV 30, held 14 January 2022, providing advice on change in dosing information).

The ACV noted current NSW data showing that the rate of people reported with COVID-19 has the highest incidence in the 10-19 year old cohort.[1]

International regulatory status

- On 3 January 2022, the US FDA extended the Emergency Use Authorization for Comirnaty to allow single booster dose to individuals 12-15 years of age who have completed a primary series with Comirnaty at least 5 months previously. The FDA review was based on data not generated by Pfizer or BioNTech.
- On 24 February 2022 the EMA announced it had recommended authorisation of booster doses of Comirnaty from 12 years of age.
- Applications are under evaluation in the UK and New Zealand.

General comments

The ACV noted the application submitted by the sponsor on 22 February 2022 contained very limited data, all generated by regulatory authorities rather than the sponsor.

Additional data are now likely to be available to the sponsor from the Israel Ministry of Health, updating the submitted data with its 15 December 2021 cut-off.

Analysis by the US CDC data uses a wider single cohort for 12-17 year olds, while in Australia there have been separate regulatory decisions on 12-15 year olds and 16-17 year olds. This added complexity to the committee's review.

Immunogenicity and efficacy

The ACV noted that no immunogenicity data had been provided from children aged 12-15 years. For adults 18 to 55 years of age, the SARS-CoV-2 neutralising GMT ratio at one month after dose 3 to one month after dose 2 was 3.29 (2 sided 97.5% CI: 2.76, 3.91), which met the 1.5 fold noninferiority criterion and suggests higher neutralising antibody concentrations.

The ACV acknowledged that the booster dose was likely to be immunogenic (for an unknown duration), effective and safe relative to dose 2, based on data in older age groups, doses 1 and 2 in the 12-15 year age group, and US CDC data. The ACV noted that severely immunocompromised persons aged 12 years and older may have completed a three dose primary series.

Safety

The ACV commented that the Israeli data disclosed a much lower rate of reporting of any adverse events (14.9 per 100,000 doses) than has been observed in Australia (see TGA COVID-19 vaccine weekly safety reports[2] and NCIRS data[3]). This raised the concern that there may be significant under-ascertainment of adverse events in passive reporting systems in Israel. Additionally, the submitted data only reported on less than 7000 children in this age group who had received a third dose, such that rare but significant events would not be expected to be detected in this number of children.

US data recently released (see Hause et al) from persons aged 12-17 years who received a homologous Comirnaty booster showed that adverse reactions were generally similar between dose 2 and booster dose 3, other than inability to go to school or work (which was higher after

[1] https://www.health.nsw.gov au/Infectious/covid-19/Documents/weekly-covid-overview-20220312.pdf
[2] See COVID-19 vaccine weekly safety reports
https://www.tga.gov.au/covid-19-vaccine-safety-monitoring-and-reporting
[3] https://ausvaxsafety.org.au/pfizer-covid-19-vaccine-paediatric-formulation-5-11-years/child-participants

dose 3). The reporting rate of confirmed cases of myocarditis among adolescent boys after Comirnaty booster dose vaccination (11.4 per million doses administered) was lower than for following dose 2 for males aged 12–15 years (70.7 per million doses administered) or 16–17 years (105.9 per million doses administered) but higher than for following dose 1 for males aged 12-15 years (7 per million doses administered).

ACV advice to the Delegate

The ACV advised the following in response to the Delegate's specific requests for advice:

1. Does ACV agree that a booster dose of Comirnaty may be administered in individuals 12 years of age and older, based on extrapolation from data in adults 18 to 55 years of age?

The ACV expressed reservations about the lack of data, a likely very small benefit against severe disease, and limited safety data from the USA and Israel.

The risk of myocarditis is hard to quantify, given the sponsor's reliance on observational Israeli data from only six thousand children. Based on US CDC data, the rate of myocarditis appeared to be lower after the booster dose compared to after second dose.

However, the benefit-risk is likely to be positive for some groups within the 12-15 year age group, for example, children at high risk of severe COVID-19 due to underlying medical conditions.

The ACV advised that the statement in the approved indication, that use of this vaccine should be in accordance with official recommendations, applies to the use of booster doses as well as the primary series doses. Official recommendations, such as from ATAGI, may reflect changing public health contexts and individual clinical situations (e.g., may favour use only in 12-15 year olds at high-risk of severe disease).

The ACV considered that the availability of booster doses may be important in the event of emergence of more transmissible or severe SARS-CoV-2 variants of concern.

The ACV agreed that a booster dose of Comirnaty may be administered in individuals 12 years of age and older, based on extrapolation from data in adults 18 to 55 years of age?

2. Does ACV agree with the product information changes proposed by the sponsor?

The ACV agreed with the product information changes proposed by the sponsor.

Additional changes should be considered:

- articulate that there are key gaps in the available data and there is no immunogenicity data in this age group
- Section 4.4/General recommendations/Myocarditis and pericarditis: mention potential for myocarditis after booster dose
- Section 4.4/Paediatric use: mention potential for myocarditis
- Section 5.1/Clinical trials/ Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses: specify the dominant SARS-CoV-2 variant at the time of the efficacy study.

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

The ACV advised that rigorous post-marketing monitoring is required, such as the monthly safety summary reports. This is consistent with the provisional registration status of the vaccine.

The ACV advised that updated data from the Israel and US CDC should be obtained and considered, given the minimal data provided by the sponsor.

The ACV noted that communication of any TGA decision needed to make clear that registration for use as a booster does not imply a booster dose is necessary or desirable for use across the Australian population aged 12-15 years.

ACV conclusion

The ACV supported the approval of changes to the Product Information of Comirnaty to include a booster (third) dose for persons 12 years and older, based on extrapolation from older age groups. This does not imply a booster dose is necessary or desirable for use across the Australian population aged 12-15 years.

The use and timing of Comirnaty booster in 12-15 year olds should be in accordance with official recommendations.

Ratified and sent to the sponsor on 30 March 2022

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