Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Vaccines Meeting 27 Minutes on Item 2.3 Tozinameran (formerly BNT162b2 [mRNA])

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

December 2021

TGA Health Safety Regulation

Contents

Submission details

Type of submission:	Extension of indication to include 5 to <12 years of age / New strength / New formulation
Product name:	Comirnaty
Active ingredient:	tozinameran (formerly BNT162b2 [mRNA])
Submission number:	PM-2021-05012-1-2
Dose form:	Suspension for injection
Strength:	10 microgram per 0.2 mL injection, for individuals 5-11 years of age 30 microgram per 0.3 mL injection, for individuals 12 years and older
Approved indication:	COMIRNATY (BNT162b2 [mRNA]) 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 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.
Indication proposed by sponsor:	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:	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 (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, 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.

Dosage proposed by sponsor:

Individuals 12 years of age and older

COMIRNATY Ready To Use Multidose (For Age 12 Years and Above, Do Not Dilute) is administered intramuscularly as a primary course of 2 doses (30 micrograms/0.3 mL) at least 21 days apart. .A booster dose (third dose) of COMIRNATY Ready To Use Multidose (For Age 12 Years and Above, Do Not Dilute) 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 dose (third dose) of COMIRNATY Ready To Use Multidose (For Age 12 Years and Above, Do Not Dilute) should be made based on available vaccine safety and effectiveness data, in accordance with official recommendations.

Doses of COMIRNATY (tozinameran) COVID-19 VACCINE [Tris/Sucrose Presentation] (30 micrograms/dose) and COMIRNATY (BNT162b2 [mRNA]) COVID-19 VACCINE (30 micrograms/dose) are considered interchangeable.

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.

Individuals 5 to <12 years of age

COMIRNATY Dilute To Use Multidose (For Age 5 to <12 Years) is administered intramuscularly as a primary course of 2 doses (10 micrograms/0.2 mL each) at least 21 days apart.

Documents considered by ACV

The ACV considered the following documentation:

A1 Delegate - Request for ACV advice and overview – dated 19 November 2021[1]
A1a Sponsor – C4591007 - Interim Clinical Study Report Body – version dated 30 September2021
A1b Sponsor – Clinical overview – 5 to 12 years – approved 5 October 2021
A2 Sponsor - application letter dated 29 October 2021
A3 Sponsor – pre-ACV response - response

[1] The Delegate's Overview was provided prior to the Quality Summary (Module 3) becoming available and was titled 'draft'. The ACV was not provided with a Quality Summary.

A3a	Sponsor – pre-ACV response - adverse reactions update
A3b	Sponsor – pre-ACV response – comments on PI
A3c	Sponsor – pre-ACV response – foreign regulatory status
A3d	Sponsor – pre-ACV response – comments on foreign PI
M5	TGA - Clinical - evaluation report – dated 19 November 2021
RMP	TGA – Risk Management Plan – evaluation report - dated 19 November 2021
PI	Product Information – clean and annotated – from pre-ACV response
CMI	Consumer Medicine Information – clean and annotated – from pre-ACV response
CAN	Canadian product monograph - dated 19 November 2021 - from pre-ACV response
USAo	USA prescribing information for emergency use authorization – 5-12 years ready to use "orange" - dated 29 October 2021 - from pre-ACV response
USAg	USA prescribing information for emergency use authorization – 12+ years ready to use "grey" - dated 19 November 2021 - from pre-ACV response
USAp	USA prescribing information for emergency use authorization – 12+ years requires dilution "purple" - dated 19 November 2021 - from pre-ACV response

Public materials discussed at the meeting included:

Oliver S. Evidence to Recommendations Framework: Pfizer-BioNTech COVID-19 vaccine in children aged 5-11 years. ACIP 2 November 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/08-COVID-Oliver-508.pdf

Gurtman A. BNT162b2(COVID-19 Vaccine, mRNA) Vaccine – in Individuals 5 to <12 years of age. ACIP 2 November 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/02-COVID-Gurtman-508.pdf

Oster M. mRNA COVID-19. Vaccine-Associated Myocarditis. ACIP 2 November 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/04-COVID-Oster-508.pdf

Su JR. Myopericarditis following COVID-19 vaccination: Updates from the Vaccine Adverse Event Reporting System (VAERS). ACIP 21 October 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf

Patel T, Kelleman M, West Z, et l. Comparison of MIS-C related myocarditis, classic viral myocarditis, and COVID-19 vaccine related myocarditis in children. Preprint posted 7 October 2021.
https://www.medrxiv.org/content/10.1101/2021.10.05.21264581v1.full.pdf

Australian Government. COVID-19 Australia: Epidemiology Report 54, reporting period ending 7 November 2021. https://doi.org/10.33321/cdi.2021.45.62

Delegate's Overview

Delegate's summary of issues

The Delegate of the Secretary of the Department of Health identified the following in their request for ACV advice:

The sponsor is proposing extension of indication for Comirnaty to children of 5-11 years of age. The sponsor is also proposing to use a new formulation (using TRIS[2] buffer, replacing phosphate buffered saline [PBS] buffer) for Comirnaty in the proposed age group. However, the pivotal study was conducted using the old formulation (PBS).

The sponsor has proposed that the new formulation will subsequently replace the currently available formulation in Australia for all age groups. This has resulted in extensive changes in the product information, including storage and dilution requirements. This can lead to significant confusion, especially if the current vaccine stock (PBS buffer formulation) is also being used simultaneously.

The delegate is of the view that there is a favourable benefit-risk balance for the use of this vaccine in the 5-11 years age population and the submitted data has satisfied the regulatory requirement for the extension of provisional registration to individuals to this age group.

Pivotal phase 1/2/3 study C4591007 provides the data for vaccine's dose finding, efficacy, immunogenicity and safety in 5-11 years (this is part of the 6 months-11 years drug development plan).

The vaccine produced overall local and systemic reactogenicity similar to other age groups. However, sample size for 5-11 years age group is much smaller in comparison to the adult trial (C4591001).

Rare cases of myocarditis and pericarditis after mRNA vaccines have been reported in the adolescent and young adult population, mainly during the post market surveillance (highest frequency in males aged 12–29 years, following 2nd dose).This has been discussed with previous (adolescent) submission. No case of myocarditis/pericarditis was reported in study C4591007. However, the safety sample size is very small and the post approval safety reports will be crucial to monitor this.

Limitations of the current data include:

- Safety follow up is currently limited to median 2.4 months post Dose 2 in cohort 1 and 2.4 weeks for the safety expansion cohort.
- Safety sample size is small.
- The duration of immune response and vaccine protection is not currently known in the proposed age group.
- Vaccine efficacy against asymptomatic infection and viral transmission are not known for the proposed age group.
- The data in immunocompromised individuals are lacking.
- Efficacy against the currently circulating variants of concern is not known yet.

Pharmacovigilance activities and post-market studies have been proposed to address these limitations.

The sponsor has also proposed two other variations within the same application:

- major variation [change in strength and dosage], to present 2 new strengths with different fill volumes, to support vaccination of different age groups with dosages of either 30 μg (≥ 12 years of age) or 10 μg (5-11 years of age)

[2] Tris is a synonym of Trometamol, which is the Australian Approved Name that appears in the list of excipients in the PI.

- change in formulation, to change from a PBS/sucrose buffered formulation to a Tris/sucrose buffered formulation that can be used in all approved age groups.

Delegate's preliminary view

While a decision is yet to be made, at this stage [19 November 2021] the Delegate is inclined to approve the proposed extension of indications.

If the extension of indication is approved, conditions for provisional registration will be imposed.

Updated following meeting: Module 3 evaluation is now complete and there are no pending quality related issues for this submission. The Module 3 evaluator has proposed Batch Release Testing and Compliance conditions for use of COMIRNATY in the proposed extension of indication in 5-11 years age group.

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

1. Based on the evidence at this point in time, does ACV consider that there is a favourable benefit-risk balance for the use of this vaccine in the 5-11 years population and the submitted data has satisfied the regulatory requirement for the extension of provisional registration to COMIRNATY (tozinameran) in this age group? Especially in view of the absence of a confirmed immunogenicity correlate of protection and only short term safety data?
2. Can the ACV comment on overall Safety in this age group? Please also advise on safety in children, especially in view of the pharmacovigilance reports of myocarditis and pericarditis in adolescents and young adults.
3. Can the ACV comment on the proposed pharmacovigilance activities? Are any additional risk mitigation strategies required? Especially in view of the risk of febrile seizure in youngest of the proposed age group (5-6 years age).
4. Does ACV envisage any practical /clinical issues with use of new Tris/Sucrose buffer formulation in 5-11 years?
    a. Of note, both Phase 1 and phase2/3 clinical trials were conducted using old PBS buffer formulation and the sponsor is proposing exclusive use of new Tris/sucrose buffer formulation for the 5-11 years age. No clinical data is provided, comparing the two formulations.

ACV discussion

General comments

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 this extension of indication).

The ACV also noted the dosing changes related to the booster dose and third dose in the primary series for immunocompromised persons. (See ACV 26, held 25 October 2021, providing advice on these PI changes).

The ACV discussed the epidemiology of COVID-19 in children aged 5 years and over. The committee understood that to 10 October2021 no child under 11 years of age had died of COVID-19 in Australia. One child under 10 years of age has died following a COVID-19 diagnosis but it is understood that COVID-19 was not the cause of death. Children in Australia with COVID-19 rarely required ICU care (<0.1%).

International regulatory status of use in children aged 5 years and over

The ACV noted information on the international regulatory status of use in children aged 5 years and over:

- The FDA issued an Emergency Use Authorization on 29 October 2021
- Notice of Compliance granted by Health Canada on 19 November 2021
- The EMA granted conditional marketing authorization on 25 November 2021
- Evaluations are in progress in New Zealand and Switzerland.

Efficacy

Pivotal phase 1/2/3 study C4591007 included the following points.

- At Day 7 post-Dose 2, the GMTs were similar across the tested dose levels: 4162.6 (95% CI: 2584.7, 6704.0) in the 10 μg group and 4583.4 (95% CI: 2802.9, 7494.8) in the 20 μg group.
- Phase 2/3 used the PBS formulation, administering 10 μg with a 21-day interval to dose 2. Participants could have a range of co-morbidity, including prior SARS-CoV-2 infection. Including a safety expansion group, 1591 children received 10 μg Comirnaty.
- The GMR of 5 to < 12 year of age participants' GMTs relative to those of 16-25 years of age participants was 1.04 (95% CI: 0.93, 1.18). This met the immunobridging objective, which served as a surrogate for efficacy. An immunological correlate of protection is not yet established.
- Responses by age within the 5-11 year age range were comparable.
- A subset / additional [this was not clear to the committee] 750 children are to be enrolled to provide samples for evaluation of troponin I, a marker of myocarditis.

The ACV noted that the absence of a controlled clinical study using the Tris/sucrose formulation proposed for provisional registration may contribute to vaccine hesitancy.

Safety

The ACV noted that all reported serious adverse events were deemed unrelated to the vaccine, while noting that the study was not powered to detect rare events. No allergic event was reported after either dose 1 or dose 2 within 30 minutes after vaccination.

Pain at injection site was the most common reaction and occurred at similar frequencies (>70%) and intensities post-dose 1 and post-dose 2. Redness and swelling were less frequent (<20%) with higher frequency post-dose 2.

The highest rate of fever (6.9%) was observed after dose 2 in children who were SARS-CoV-2 negative at baseline.

To date, post-market experience in the USA relates mainly to first doses. To date, there is no signal of myocarditis following second doses.

The ACV noted that information for parents/carers will need to highlight the adverse events and their severity that warrant seeking medical attention.

Consideration should be given to utilisation of linked data assets to generate vaccine attributable risk estimates on myocarditis and pericarditis in people post vaccination, especially children, including long-term follow-up.

Quality

The ACV noted that the Tris/sucrose formulation can be stored at refrigerator temperature for up to 10 weeks prior to use.

Risk management including medication errors

The ACV noted that in the phase 1 study the observed reactogenicity in the initial 4/16 participants assigned the 30 μg dose (the adult dose) led to the discontinuation of this dose level. There is a clear risk of adverse events from administration of the adult dose in error. Under the clinical trial conditions, dosing errors occurred in 3% of doses administered.

The ACV noted that it is anticipated that there will be concurrent availability and transition from 'purple' to 'grey' and introduction of 'orange' formulations, with different requirements for dilution and storage times. This creates the potential for confusion and administration errors and will need to be well managed. This will include clear communication to providers, specific training and education, and the consideration of systems to ensure safe administration.

ACV advice to the Delegate

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

1. **Based on the evidence at this point in time, does ACV consider that there is a favourable benefit-risk balance for the use of this vaccine in the 5-11 years population and the submitted data has satisfied the regulatory requirement for the extension of provisional registration to COMIRNATY (tozinameran) in this age group? Especially in view of the absence of a confirmed immunogenicity correlate of protection and only short term safety data?**

The ACV agreed there is favourable benefit-risk balance in the 5-11 year old age group. The ACV noted that there are likely to be both direct and indirect benefits to this age group and the broader community associated with vaccination of this age group.

The ACV advised that the available evidence, that demonstrated immunogenicity and efficacy against infection, supports use in the population aged 5-11 years. The ACV commented there is an observed association between high levels of neutralising antibodies and efficacy although an immunological correlate of protection is yet to be well defined.

Immunogenicity against the Delta strain was considered by the ACV, and although slightly diminished compared to the original strain, there still appeared to be significant neutralisation antibody activity within this small subset of 34 participants. Vaccine-induced immunity against new variants, such as the recently reported Omicron variant, is not yet known.

2. **Can the ACV comment on overall Safety in this age group? Please also advise on safety in children, especially in view of the pharmacovigilance reports of myocarditis and pericarditis in adolescents and young adults.**

The ACV considered both the clinical trial data and preliminary post-market safety experience in the 5-11 year age group. The ACV commented that there are no safety signals of note in the United States as yet, however these data are predominantly based on available information following the first dose.

While the ACV advised the overall long-term safety data in children are relatively limited, they were of the view that there are sufficient data to make a positive recommendation, noting the considerable safety data in older age groups. The ACV agreed that the reactogenicity profile is acceptable.

The ACV noted that there were low rates of any serious adverse events (SAEs), a small number of withdrawals due to adverse events (AEs) and no deaths in the clinical trial.

The ACV noted that no cases of myocarditis were reported in the clinical trial, although the safety population was not powered to detect cases at the rates reported in older age groups. The ACV advised that the risk of myocarditis in this age group is reasonably expected to be lower than in older age groups due to the lower dose. The ACV noted that the rate of vaccine-associated myocarditis in 12-15 year olds appears to be lower than that in 16-17 year olds. It was also noted that the background rate of myocarditis of any cause is lower in the 5-11 year age group than in older children.

The ACV agreed that is important to monitor this potential rare but clinically important adverse event in the wider population. The ACV expressed significant interest in the anticipated provision by the sponsor of the troponin data from clinical trial participants, as this will assist with increasing the understanding of the safety profile of this vaccine.

The ACV discussed the incidence of lymphadenopathy, which was reported at 0.7% in the vaccine group and not reported in the placebo group. ACV noted that all cases were mild. The ACV agreed that is important to monitor this potential adverse event in the wider population.

The ACV was reassured that further safety data is currently being collected as part of the safety expansion study consisting of 2379 participants. Additionally, data are accumulating from a variety of post-marketing surveillance systems.

3. Can the ACV comment on the proposed pharmacovigilance activities? Are any additional risk mitigation strategies required? Especially in view of the risk of febrile seizure in youngest of the proposed age group (5-6 years age).

The ACV reiterated the importance of post-market monitoring for all adverse events, particularly severe adverse events such as myocarditis and pericarditis. The ACV agreed that augmented capabilities for timely investigation, data collation and reporting is important as the program is rolled out to a broader population. This should include long term follow up of clinical outcomes for those who experience serious adverse events following immunisation.

The ACV did not express concern about the risk of febrile seizures in the proposed age group. The ACV noted the risk of febrile seizures is low in the proposed age range, however the risk of fever in select children with underlying medical conditions warrants monitoring. The ACV also noted that there were only rare reported febrile seizure events in US surveillance to date. Specific guidance should be provided to parents to ensure they are aware of potential adverse events following vaccination, what signs and symptoms to look for, and how to respond.

4. Does ACV envisage any practical /clinical issues with use of new Tris/Sucrose buffer formulation in 5-11 years?

a. Of note, both Phase 1 and phase2/3 clinical trials were conducted using old PBS buffer formulation and the sponsor is proposing exclusive use of new

Tris/sucrose buffer formulation for the 5-11 years age. No clinical data is provided, comparing the two formulations.

The ACV noted the previous PBS buffered formulation (purple top) and the new Tris/sucrose buffer formulation for adults and children 12+ years (grey top) and 5-11 year paediatric group (orange top).

The ACV did not express any significant concerns with the lack of clinical data being provided to compare the two formulations. The ACV noted the positive benefits of the Tris/sucrose buffer formulation in relation to the extended fridge shelf life. The ACV noted that Tris buffers are widely used in other vaccines and this change in the buffer is not expected to have any safety implications; this may require specific communication to consumers.

The ACV noted that confusion could occur as a result of multiple formulations of the same product being available concurrently and strongly emphasised the importance of having robust guidance, labelling, training, communication and a range of other strategies to clearly convey these changes to both providers and consumers.

The ACV highlighted that such risk mitigation strategies will be important to ensure safe program delivery.

ACV conclusion

The ACV considered Comirnaty to have an overall positive benefit-risk profile, and therefore supports provisional approval for the following:

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.

Ratified and sent to the sponsor on 6 December 2021

Therapeutic Goods Administration

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