Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

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

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

7 September 2022

Contents

Submission details

Type of submission:	Extension of indication – primary series for individuals 6 months to 5 years of age New strength - 3 microgram/0.2 mL
Product name:	Comirnaty
Active ingredient:	Tozinameran (formerly BNT162b2 [mRNA])
Submission number:	PM-2022-03129-1-2
Strength / dose form:	3 microgram per 0.2 mL dose, embedded in lipid nanoparticles, as Concentrate for suspension for injection
Proposed indication (changes from approved indication in bold italic underline):	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 ***6 months*** ~~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.
Proposed dosage:	*Individuals 6 months to <5 years of age* COMIRNATY Dilute To Use Multidose (For Age 6 months to <5 Years) is administered intramuscularly as a primary course of 3 doses (3 micrograms/0.2 mL each). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties). Children who will turn from 4 years to 5 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series. COMIRNATY Dilute To Use Multidose (For Age 6 months to <5 Years) cannot be used in individuals 5 years of age and older.

Documents submitted for ACV consideration

The ACV considered the following documentation:

A1 Delegate's Overview – 30 August 2022[1]
A2 application letter – 25 July 2022
A3 Sponsor – pre-ACV response
response
adverse reactions update
comments on PI
foreign regulatory status
comments on foreign PI
M5 Clinical evaluation report -
RMP Risk Management Plan evaluation report
PI Product Information – clean and annotated – from pre-ACV response
CMI Consumer Medicine Information – clean and annotated – from pre-ACV response
USA USA emergency use fact sheet – maroon vial – from pre-ACV response

Public domain information:

- Farrar DS, Drouin O, Moore Hepburn C, et al. Risk factors for severe COVID-19 in hospitalized children in Canada: A national prospective study from March 2020-May 2021. Lancet Reg Health Am 2022;15:100337. doi: 10.1016/j.lana.2022.100337
- Hause AM, Marquez P, Zhang B, et al. COVID-19 mRNA Vaccine Safety Among Children Aged 6 Months–5 Years — United States, June 18, 2022–August 21, 2022. MMWR 2 September 2022
- Presentations from Vaccines and Related Biological Products Advisory Committee held 15 June 2022, including by Gruber and Wollersheim and FDA briefing documents
- Presentations from ACIP meeting held 18 June 2022, including by Hall
- Presentations from ACIP meeting held 1 September 2022, including by Shimabukuro
- Press Release 'Pfizer and BioNTech Announce Updated COVID-19 Vaccine Data Supporting Efficacy in Children 6 Months through 4 Years of Age', 23 August 2022 https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-updated-covid-19-vaccine-data

Delegate's Overview

Delegate's summary of issues

The delegate is of the view that there is a favourable benefit-risk balance for the use of this vaccine in the infant population and the submitted data has satisfied the regulatory requirement for the extension of provisional registration to individual 6 months to < 5 years of age.

Summary of data

- In phase 1 of Study C4591007 safety and immunogenicity data led to the selection of 3 microgram dose to balance tolerability and immune responses.
- In phase 2/3 of Study C4591007 there were 2750 participants aged 2 to < 5 years (1835 BNT162b2, 915 placebo) and 1776 participants aged 6 months to < 2 years (1178 BNT162b2, 598 placebo).

[1] A typographic error was identified on page 8 of 58 of the Delegate Overview, which should read 'There are no objections, from a sterility point of view, to approval of the application to register COMIRNATY (tozinameran) COVID-19 VACCINE 3 µg/0.2 mL concentrated suspension for injection vial.'

- Following a 2-dose regimen, non-inferiority of immunobridging based on seroresponse was not declared for children 2 to <5 years of age, leading to a 3-dose regimen for children <5 years of age.
- Immunobridging criteria were met for both GMR and seroresponse in both age groups following 3 doses of vaccine.
- Similar neutralizing responses to Omicron were observed across age groups one month after the third dose for individuals aged 6 months to < 2 years, 2-< 5years and adults 18-50 years.
- VE appears favourable (75-82%), while noting small sample size (only 10 cases of COVID -19).
- Adverse events were low, and slightly higher in the younger cohort; no new safety signals were identified.
- Of study participants, about one-third received 3 vaccine doses of BNT162b2.
- The study has only short term follow up (1.3 months following dose 3 in children 6-months to 23-months of age).

Delegate's preliminary view

While a decision is yet to be made, at this stage the Delegate is inclined to approve the proposed extension of indication and new lower strength formulation.

The final decision will be made following the ACV discussion. If approved, Conditions for Provisional Registration would be applied.

Advice sought by Delegate of the Secretary of the Department of Health and Aged Care

1. Does ACV consider that there is a favourable benefit-risk balance for the extension of provisional registration to individuals 6 months to < 5 years of age?
2. Does the ACV have any advice of the 3-dosing schedule as a primary vaccination course in these age groups?
3. The committee is also requested to provide advice on any other issues that may be relevant to a decision on whether or not to approve this application

ACV discussion

Environment

The ACV noted that Comirnaty was first provisionally registered on the ARTG on 25 January 2021 for use in persons from 16 years of age. Extensions of indication for primary series vaccination, new formulation and booster doses have been incrementally approved.

The ACV noted the Comirnaty range will consist of:

- PBS buffered formulation for adults and children 12+ years that <u>does</u> require dilution before use (purple top; 30 microgram/0.3 mL)
- Tris/sucrose buffer formulation for adults and children 12+ years that <u>does not</u> require dilution (grey top; dose 30 microgram/0.3 mL)

- Tris/sucrose buffer formulation for 5 to <12-year-olds that does require dilution before use (orange top; dose 10 microgram/0.2 mL)
- Tris/sucrose buffer formulation for infants and children 6 months to <5 years that does require dilution (maroon top; dose 3 microgram/0.2 mL).

The ACV noted differences between the proposed dose regimen for Comirnaty (3 doses of 3 micrograms at intervals of 3 weeks and at least 8 weeks in individuals 6 months to less than 5 years of age) and the approved dose regimen for Moderna's Spikevax (2 doses of 25 micrograms at interval of 28 days for individuals 6 months to less than 6 years of age).

International regulatory status

- On 17 June 2022 the US FDA issued an Emergency Use Authorization for Comirnaty to for primary series in individuals 6 months of age and older.
- Submissions are under evaluation in the EU, New Zealand, Canada[2], Singapore and Switzerland.

General comments

The ACV discussed the increasing complexity and consequential risks within the Comirnaty range of vaccines and the COVID-19 range of vaccines, highlighting:

- inclusion of information on a presentation that is not supplied (grey lid) is not helpful[3]
- interval between doses will be influenced by practicalities such as vaccination of family members of different ages at the same medical appointment; disruption of 3-dose schedule due to concurrent illness.

The ACV noted recent Australian data on cases, hospitalisation and deaths following SARS-CoV-2 infection in infants and children.

The ACV noted that the proportions of the cohorts who were seropositive at commencement of the clinical trial (March 2021) were low, at 4% (6 of 145) children aged 6-months to 2-years and 6% (13 of 217) children aged 2-4-years of age. This may not reflect the situations in Australia and internationally, with ever-increasing proportions of the population having been infected with SARS-CoV-2.

Immunogenicity and efficacy

The ACV highlighted the following points for Study C4591007.

[2] Approved in Canada on 9 September 2022.

[3] The ACV 27 minutes included:

> The ACV noted that it is anticipated that there will be concurrent availability and transition **from 'purple' to 'grey'** and introduction of 'orange' [lidded vials and] formulations, with different requirements for dilution and storage times. This creates the potential for confusion and administration errors …

Subsequent to ACV 37 meeting, Pfizer advised:

> The ACV 27 minutes from November 2021 were accurate with the understanding at the time.
> Pfizer is yet to commence supply of the grey cap [tris/sucrose formulation] presentation.
> The COMIRNATY presentation for individuals 12 years and over has always been the purple-cap vials.
> Pfizer will seek to minimise this period, however, please note that even if the transition to grey cap product results in no further supply of purple cap product, the Commonwealth may still have significant quantities of purple cap product in storage and may choose to use this on an ongoing basis.

- One-month post-dose 3 in participants without prior infection showed GMTs similar (if not above) levels achieved in young adults: 1535.2 (95% CI 1388.2, 1697.8) in children 2-4 years of age; 1180.0 (95% CI 1066.6, 1305.4) in young adults.
- Immunobridging analysis after dose 3 only included a small subset of children: n=82 (6-23 months) and n=143 (2-5 years).
- Neutralisation titre analyses were against ancestral strain, not the Omicron variant.
- Higher GMT at 1 month after dose 3 (by factor of 2.3) were observed in infants and children who were seropositive at commencement of the trial.
- With additional follow-up, VE has fallen to 73.2% (95% CI: 43.8%, 87.6%) based on analysis from 34 cases occurring at least 7 days following a 3-dose regimen among baseline seronegative children aged 6-months to 4-years of age.

The 3-dose regimen was informed by the clinical study and real-world data showing a third dose was likely necessary to provide a high level of protection against Omicron variants.

The ACV noted that the dose interval of 21 days between first and second doses, and at least 8 weeks to the third dose (median 12.9 weeks in children 6-months to 2-years of age; range 8 to 20 weeks) could be construed as a 2-dose primary series with booster dose.

Safety

The ACV noted that the vaccine was generally well tolerated. The proportions of participants reporting adverse events who were sero-positive at baseline was similar to participants who were sero-negative at baseline.

Most local adverse events were mild or moderate. No Grade 4 event (local or systemic) was reported after any dose. The most commonly reported adverse events were consistent with local and systemic reactogenicity and/or events frequently reported in this age group (e.g., infections and injuries).

No vaccine-related events of anaphylaxis occurred. There were more cases of lymphadenopathy following Comirnaty than placebo, but the number of cases was small. One infant aged 6-months was reported to have a serious adverse event (eye rolling upwards) that occurred 2 days after Dose 2; febrile seizure related to vaccination cannot be definitively excluded based on available information.

The trial size was too small to provide data on rare outcomes post vaccination, such as myocarditis.

There was a comment that monitoring systemic reactions such as fever within 7 days of vaccination is probably not as sensitive to the effect of the vaccine administration as would be monitoring systemic reactions within 2 days.

There was no suggestion of sequential reactogenicity increasing with increased dose number.

The ACV noted the absence of co-administration studies with influenza vaccine or the standard early childhood vaccines.

The ACV noted the lack of immunogenicity and safety date in immunocompromised individuals, although these infants and children are likely to be more at risk from severe COVID-19.

The ACV noted with concern the VAERS data (as of 21 August 2022; 496 reports) on Comirnaty vaccination in children 6-months to 4 years of age showing incorrect dose administered (18% of reports), product administered to patient of inappropriate age (11%), product preparation issues (10%) and wrong product administered (7%). VAERS

data (as of 21 August 2022; 521 reports) on Spikevax vaccination in children 6-months to 5 years of age show expired product administered (7% of reports) and incorrect dose administered (7%).

ACV advice to the Delegate

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

1. Does ACV consider that there is a favourable benefit-risk balance for the extension of provisional registration to individuals 6 months to < 5 years of age?

The ACV advised that there is a favourable benefit-risk balance to individuals 6 months to less than 5 years of age. This is based on immunogenicity and preliminary efficacy and safety data from the administration of Comirnaty, compared with the rare risk of hospitalisation and serious outcomes in this age group.

The ACV was of the view that the greatest benefit is anticipated to be in infants and children who are at high risk of developing severe disease (i.e., children with severe immunocompromise or significant respiratory/cardiac disease). The ACV further advised that the use of this vaccine should be in line with official guidelines, such as developed by the Australian Technical Advisory Group on Immunisation (ATAGI).

The ACV noted that the study was not powered to detect rare events such as myocarditis and was supportive of robust post-marketing safety monitoring.

2. Does the ACV have any advice of the 3-dosing schedule as a primary vaccination course in these age groups?

The ACV advised that the basis for inclusion of a third dose in this primary schedule was appropriately justified in the application.

The ACV noted that GMTs from the immunobridging subset showed similar (or higher) responses to those achieved in young adults. However, this is not entirely predictive of level of protection.

The ACV noted that the completion rate of a 3-dose primary series may be low. The ACV advised that ongoing studies that are used to provide efficacy estimates should separately address efficacy following 1, 2 and 3 doses.

The ACV noted that a significant proportion of Australian children are likely to have had SARS-CoV-2 infection before receiving vaccination.

The ACV noted that each vaccination is an opportunity for a medication error to occur (such as incorrect dose or product), and so a 3-dose regimen with varying intervals between doses provides a greater challenge to quality use of medicines than a 2-dose regimen.

The ACV highlighted the potential for administration of a COVID-19 vaccine to disrupt the well-established early childhood vaccination schedules for other childhood diseases. In the absence of co-administration trials, studies monitoring potential interactions should be undertaken.

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

The ACV noted confusion and medication errors are likely to occur in Australia, and have already been observed in the USA, due to multiple formulations with the same brand names being available concurrently. The ACV strongly emphasised the importance of having robust guidance, labelling, training, communications, and a range of other strategies to clearly convey product differences to both providers and consumers. The ACV

highlighted that such risk mitigation strategies will be important to ensure safe program delivery. Further, planning for ascertainment of medication errors is also necessary.

The ACV noted that there was no dose-ranging data available to inform the counselling of parent/carer if a child is administered an overdose of vaccine.

ACV conclusion

The ACV considered this product to have an overall positive benefit-risk profile for the 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 6 months 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 15 September 2022; minor revisions, re-ratified and sent to the sponsor on 19 September 2022.

Therapeutic Goods Administration

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