Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Vaccines Meeting 22 Minutes on Item 2.1 BNT162b2 [mRNA] COVID-19 vaccine

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

16 June 2021, adjourned to 5 July 2021

TGA Health Safety Regulation

Contents

Submission details

Type of submission:	Extension of indication Provisional approval determination for this extension of indication granted 11 May 2021 Provisional registration of the vaccine for use in persons 16 years and older approved 25 January 2021
Product name:	Comirnaty
Active ingredient:	BNT162b2 [mRNA]
Submission number:	PM-2021-02187-1
Proposed dose form:	Concentrated suspension for injection
Proposed strength:	30 microgram per 0.3 mL injection
Initial indication proposed by the sponsor:	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.
Indication proposed by Delegate:	COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below: Active immunisation to prevent coronavirus disease (COVID-19) caused by SARS-CoV-2 virus, 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.
Proposed dosage:	Intramuscular administration of two doses, at least 21 days apart.

Documents submitted for ACV consideration

The ACV considered the following documentation:

Provided 11 June

A1 Delegate - request for ACV advice and overview – 'Delegate's Overview'
A2 Sponsor - application letter dated 28 May 2021
A2a ACV – Minutes of item 2.1 of 15 January 2021 meeting of ACV
M5 TGA - Clinical Evaluation report – round 1
M5a TGA – Monthly summary safety report review of April 2021
M5b Sponsor – Safety evaluation of myocarditis and pericarditis for reporting period 1 April 2021 to 29 April 2021 – also called Appendix 3.7 of Summary Monthly Safety Report (SMSR) 5 for April 2021

M5c TGA – Clinical evaluation report for PM-2020-05464-1-2 (post-approval commitment by sponsor to submit a safety analysis at 6 months post-Dose 2 from study C4591001 (Phase 2/3)) – DRAFT report dated 9 June 2021
M5d Sponsor – interim adolescent – report body – also called Interim Clinical Study Report-Protocol C4591001 - dated 14 April 2021
M5e Sponsor – Periodic safety update report – also called Summary Monthly Safety Report (SMSR) 5 - April 2021
RMP TGA - Risk Management Plan - Evaluation Report - round 1

Provided 15 June

A3 Sponsor - pre-ACV response – cover letter, and response
A3a Sponsor - pre-ACV response – adverse reactions update
A3b Sponsor - pre-ACV response – Safety evaluation myocarditis and pericarditis – May 2021
A3c Sponsor – pre-ACV response – comments on product information
A3d Sponsor – pre-ACV response – foreign status
A3e Sponsor – pre-ACV response – comment on foreign product information

PI Product Information – clean and annotated - dated 15 June 2021
CMI Consumer Medicine Information – clean and annotated

CAN Canadian product monograph – interim authorisation – dated 19 May 2021
EU European summary of product characteristics – conditional marketing approval – dated December 2020
SING Singaporean interim authorisation fact sheet – dated 25 May 2021
SWISS Swiss temporary authorisation product information – dated June 2021
UK UK's temporary authorisation healthcare professional information – dated June 2021
USA American emergency use fact sheet – dated 19 May 2021

Provided 16 June

Snapiri O, Rosenberg Danziger C, Shirman N, Weissbach A, et al. Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine. Pediatr Infect Dis J 2021;XX:00–00. DOI: 10.1097/INF.0000000000003235

Mouch SA, Roguin A, Hellou E, Ishai A, et al. Myocarditis following COVID-19 mRNA vaccination. In press. https://doi.org/10.1016/j.vaccine.2021.05.087

Marshall M, Ferguson ID, Lewis P, Jaggi P, et al. Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID- 19 Vaccination. Pediatrics 2021, prepublication release. DOI: 10.1542/peds.2021-052478

Other information considered by committee

CDC Vaccines and Related Biological Products Advisory Committee – 10 June 2021 - Meeting Presentation by Tom Shimabukuro; https://www.fda.gov/media/150054/download (accessed 16 June 2021)

Other information considered by committee following adjournment

CDC ACIP Committee – Coronavirus Disease 2019 (COVID-19) Vaccines - 23 June 2021 - Meeting Presentation Slides https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html (accessed 24 June 2021)

Delegate's Overview

Delegate's summary of issues

Data limitations/uncertainties of the submitted data include:

- The long-term efficacy and safety is not known
- The vaccine efficacy against asymptomatic infection and viral transmission is not known
- The number of adolescents in the study is not sufficient to detect vary rare adverse events
- No data are available on the co-administration with quadrivalent seasonal influenza vaccine
- Adolescents with immunodeficient status/high health risks are not specifically assessed
- The vaccine efficacy against variants of concern has not been assessed.

Rare cases of myocarditis/pericarditis following vaccination with Comirnaty have been observed in the global post-market setting. Detailed analysis of this issue is provided to the ACV by the TGA's post market evaluation team; see item 3.1 of the current meeting agenda.

Delegate's preliminary view

The Delegate is of the view that there is a favourable benefit-risk balance for the use of this vaccine in the adolescent population and the submitted data have satisfied the regulatory requirement for the extension of provisional registration to individual 12 to 15 years of age.

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

If the extension of indication was approved, approval would include Conditions for Provisional Registration, as described in Attachment 2 of the Delegate's overview.

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

1. Does ACV consider that there is a favourable benefit-risk balance for the use of this vaccine in the adolescent population and the submitted data has met the regulatory requirement for the extension of provisional registration to individuals 12 to 15 years of age?
2. There are rare cases of myocarditis and pericarditis reported following vaccination with Comirnaty in young people in the global post-market setting. Could ACV please advise:
    a. Whether these rare events would change the benefit-risk balance for the use of this vaccine in the adolescent population?
    b. Whether any regulatory action, such as adding relevant statements in the PI, should be taken at this stage?

ACV discussion

Epidemiology

As of May 2021, the ongoing SARS-CoV-2 pandemic remains a challenge to public health and economic stability worldwide. A preventive vaccine for this age group is an important public health measure.

Three vaccines are provisionally registered to prevent COVID-19: Comirnaty (for use in persons over 16 years) and COVID-19 vaccine AstraZeneca and COVID-19 vaccine Janssen (for use in persons over 16 years; the Janssen vaccine is not included in Australia's COVID-19 vaccination program).

International regulatory status of Comirnaty for persons12+ years of age

- Health Canada issued an interim authorisation on 5 May 2021
- FDA granted an Emergency Use Authorization on 10 May 2021
- Health Sciences Authority (HSA), Singapore extended an interim authorisation on 18 May 2021
- EMA extended a conditional authorisation on 28 May 2021
- Swissmedic extended temporary authorisation on 4 June 2021
- MHRA (UK) extended a temporary supply authorisation on 4 June 2021
- Germany's vaccine advisory committee StiKo recommended that only children and adolescents with pre-existing conditions be vaccinated on 11 June 2021.

Efficacy

The ACV noted:

- immunogenicity, efficacy and safety analysis for adolescents 12 to 15 years old from Study C4591001 in blinded follow-up to a data cutoff date of 13 March 2021
- immunogenicity analysis based on the non-inferiority (NI) comparison of adolescents to young adults (16-25 years of age)

The results showed that in adolescents without evidence of prior infection with SARS-CoV-2, the estimate of vaccine efficacy against the first occurrence of confirmed SARS-CoV-2 infection from 7 days post Dose 2 was 100% (95% CI: 75.3 to 100.0%). There were no cases of COVID-19 among 1,005 vaccine recipients.

Overall, efficacy was similar between the 12-15 year age cohort, and persons 16+ years.

Safety

The ACV noted the 6 months post Dose 2 safety data as part of the post approval commitment to the original provisional approval for individual older than 16 years of age.

Local and systemic reactions are essentially the same as in adults. Most common solicited reactions are pain and injection site reaction, and fatigue, headache and myalgia.

The major discussion point was around myocarditis and pericarditis. The committee noted:

- The sponsor's analysis (up to 31 May 2021) of post-market experience is that the Observed/Expected (O/E) ratios for spontaneous reports of both myocarditis and pericarditis were less than 1 across all age groups. Ratios were highest in the 18-24

age group. This analysis was based on 260 reports coded myocarditis and 235 reports coded pericarditis, including 25 reports reporting both terms.

- Preliminary myocarditis/pericarditis reports to the US's VAERS (up to 25 May 2021) total 488 (116 reports following dose 1 and 372 reports following dose 2). The O/E ratio were greater than 1 for the 16-17 age group and 18-24 age group (only 2 cases in 12-15 years age group)
  - Following the adjournment, US's VAERS (up to 11 June 2021) data continue to shows O/E ratios greater than 1, especially after dose 2 in younger age groups.
- US's Vaccine Safety Link data, from healthcare organisations, has not detected a signal for myocarditis/pericarditis. There are 7 reports post dose 2 (rate of 10.4 per million doses), and one report after first dose, in 16-39 year olds.
- Israeli analysis concluded there is a probably causal link between second mRNA COVID-19 vaccination and onset of myocarditis in males aged 16-30 years, with the highest risk in those aged 16-19 years.
- Unpublished data from Victoria on less than 10 reports.

General

The committee discussed the clinical course of non-vaccine associated myocarditis, mentioning: the clinical course is very variable in adolescent patients; ventricular function may be unaffected or severely affected; higher prevalence in males; exercise would typically be restricted for 6 months following the acute episode; there is a low threshold for transferring patients into tertiary hospitals; long term follow-up is important as problems (arrhythmias due to scarring of myocardium) may develop later in life.

The true prevalence of myocarditis is unknown, as definitive diagnostic tests are not widely available. Autoimmunity is increasingly recognised as a contributing factor.

Regulatory approvals for use in the 12-15 years age group in Israel and UK were subsequent to the emergence of the data on myocarditis after vaccination described above.

Adjournment on 16 June

The ACV informed the Delegate that relevant additional data on the risks of the vaccine in the 12-15 years age group would shortly become available from the USA CDC Advisory Committee on Immunization Practices (ACIP)[1]. The ACV would provide advice following consideration of that additional data.

ACV advice to the Delegate

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

1. **Does ACV consider that there is a favourable benefit-risk balance for the use of this vaccine in the adolescent population and the submitted data has met the regulatory requirement for the extension of provisional registration to individuals 12 to 15 years of age?**

[1] The 18 June 2021 ACIP meeting on COVID-19 vaccines was rescheduled to be included as part of the June 23-25 ACIP meeting.

The ACV advised that the benefit of the vaccine are:

- immunogenicity that is not inferior (and possibly superior) in the 12 to 15 years age group compared to older persons
- although limited, efficacy data are similar to that in young adults.
- reactogenicity is similar to that in young adults.

Risks of the vaccine in the 12-15 years age group include increase risks in myocarditis and/or pericarditis and lymphandenopathy.

Even apparently mild episodes of myocarditis may lead to long term sequelae, such as arrhythmias. However, additional data from the US suggested that the majority of cases of myocarditis and/or pericarditis after mRNA COVID-19 vaccines (both Pfizer and Moderna) analysed to date occurred in older adolescents and young adults (aged 16 to 30 years), with highest risk in younger males within days after dose 2. Most cases were mild and recovered within days with a median duration of hospitalisation of 1 day.

Health authorities in the US and other settings continue to recommend use of the vaccine in this age group and younger adolescents based on the balance of benefit over risk.

Thus, myocartitis / pericarditis is a small but significant risk of an important complication in otherwise healthy children.

Risks from COVID-19 infection in children include hospitalization (about 5%) and mechanical ventilation (about 0.25%), as well as MIS-C (Multi-inflammatory syndrome in children, also known as PIMS-TS) and 'long COVID'.

Overall, the benefit-risk is favourable for provisional approval of the vaccine. The balance or risk and benefit will depend on the epidemiology of COVID-19 disease.

The benefit-risk will be higher in adolescents at greater risk of COVID-19 disease due to pre-existing health conditions.

2. There are rare cases of myocarditis and pericarditis reported following vaccination with Comirnaty in young people in the global post-market setting, could ACV please advise:

a. Whether these rare events would change the benefit-risk balance for the use of this vaccine in the adolescent population?

The ACV advised that incidence, severity and outcome data (the true size of the signal) are still emerging.

Most cases of myocarditis and pericarditis appeared to be mild and resolve with therapy.

Information on longer term outcomes or recurrences is not available.

b. Whether any regulatory action, such as adding relevant statements in the PI, should be taken at this stage?

The ACV advised that relevant statements should be included in the PI:

- Reported events of myocarditis and pericarditis
- Risk appears to be greater in adolescents compared to older adults; in males; after the second dose
- A high index of suspicion for presentations within a risk time window – within 4 days of either first or second dose, but particularly the second dose – for people presenting with chest pain, dyspnoea, or suggestion of arrhythmia.

- Precaution for patients with a history of myocarditis or pericarditis, whether due to mRNA vaccine or not. Vaccination of such children should be considered on a case-by-case basis with specialist input, as required.

Suitable wording could be:

> *Rare cases of myocarditis and pericarditis have been reported following vaccination with Comirnaty, although a causal association is not established. Reported cases have occurred predominantly but not exclusively in male adolescents and young adults. Onset was typically within several days after vaccination, and cases have occurred more often after the second dose than the first dose. Current available data from short term follow-up suggest most individuals have had resolution of symptoms, however information regarding potential long term sequelae is not known. Clinicians should consider myocarditis and pericarditis in adolescents or young adults presenting with acute chest pain, shortness of breath, or palpitations several days after vaccination, and should consider consultation with cardiologists or referral to an emergency department for assistance with cardiac evaluation and management.*

Enhanced surveillance should be in place for myocarditis and pericarditis.

3. Other advice

The ACV suggested liaison with primary care, emergency and radiology clinical colleges and similar, regarding: recognition of presentation, specialist referral and management; availability of appropriate diagnostic tests (e.g. ECG; echocardiogram; cardiac MRI, if indicated); agreed case definitions. This should be done in conjunction with the Australian Technical Advisory Group on Immunisation, which develops clinical guidelines for immunisation use in Australia.

The ACV suggested liaison with paediatric cardiologists, including potential role in active surveillance.

ACV conclusion

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

> 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.

Ratified and sent to the sponsor 3 pm on 5 July 2021

Therapeutic Goods Administration

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