Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Vaccines Meeting 18 Minutes on Item 2.1 BNT162b2 [mRNA] COVID-19 vaccine

Proprietary Product Name: Comirnaty

Sponsor: Pfizer Australia Pty Ltd

January 2021

TGA Health Safety Regulation

Contents

Submission details 3
Documents submitted for ACV consideration 4
Delegate's Overview 5
Delegate's summary of issues 5
Delegate's preliminary view 5
Advice sought by Delegate of the Secretary of the Department of Health 5
ACV discussion 6
Epidemiology 6
Quality 6
Efficacy 6
Safety 7
Risk Management Plan 9
ACV advice to the Delegate 10
ACV conclusion 12

Submission details

Type of submission:	New biological medicine Provisional approval determination granted 14 October 2020
Product name:	Comirnaty
Active ingredient:	BNT162b2 [mRNA] [1]
Submission number:	PM-2020-05461-1-2
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 16 years of age and older
Indication proposed by Delegate:	COMIRNATY (BNT162b2[mRNA]) COVID-19 Vaccine has **provisional approval** for the indication below: Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 16 years of age and older. The vaccine should be used in accordance with official guidance in an officially declared pandemic. 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 the ongoing and post-market assessment.
Revised indication proposed by the sponsor:	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 16 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, 21 days apart.

[1] Pending decision on the International Nonproprietary Name and the Australian Approved Name.

Documents submitted for ACV consideration

The ACV considered the following documentation, provided at various times between 10 December 2020 and 15 January 2021.

A1 Delegate - request for ACV advice and overview – 'Delegate's Overview'
A1a Sponsor – clinical overview dated 3 December 2020
A1b EMA – assessment report dated 21 December 2020
A2 Sponsor - application letter dated 23 October 2020
M3 TGA - Quality – product summary
M3a TGA – Quality – evaluation report – active ingredient Drug Substance
M3b TGA – Quality – evaluation report – vaccine Drug Product
M3c TGA – Quality – draft consent for labels that do not comply with Labelling Order
M3d Sponsor – Labels for vial and 195 vial carton - European
M3e Sponsor – Labels for vial and 195 vial carton – Australian – FDA Emergency Use
M4 TGA - Nonclinical – summary and evaluation report
M4a TGA – Nonclinical comment on Supernumerary lumbar ribs
M5 TGA - Clinical - evaluation report
M5a Sponsor – C4591001 – Final Analysis Interim Synopsis
M5b Sponsor – C4591001 – Final Analysis Interim Report Body dated 3 December 2020
M5c TGA – Report on Protocol C4591001 Interim Clinical Study Report Statistical Plan
RMP TGA - Risk Management Plan (RMP) - evaluation report
RMPa Sponsor – European Risk Management Plan dated 21 December 2020
RMPb Sponsor – Australian Specific Annex to the EU-RMP dated version 0.1
PI Product Information – clean and annotated - dated 13 January 2021 - pfpcovii20121
CMI Consumer Medicine Information – clean and annotated dated 13 January 2021

The ACV considered the following documentation, provided 13 January.

A3 Sponsor – preACV response - response
A3a Sponsor – preACV response - adverse reactions update
A3b Sponsor – preACV response – comments on PI
A3c Sponsor – preACV response – overseas regulatory status
A3d Sponsor – preACV response – comments on overseas PI

Overseas product information

OS Canadian product monograph dated 9 December 2020
OS European summary of product characteristics
OS Swiss product information
OS UK information for temporary use
OS USA prescribing information for emergency use authorization

Documents provided early and superseded

PI Product Information – clean – version pfpcovii11220
PI Product Information – clean and annotated – as at 5 January 2021
CMI Consumer Medicine Information – clean – as at December 2020
CMI Consumer Medicine Information – clean and annotated – as at 5 January 2021
RMP European Risk Management Plan – dated 29 November 2020
A1aa Delegate's draft questions – as at 8 January 2021

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 clinical data to support this provisional registration are largely from Study C4591001, an ongoing Phase 1/2/3, randomized, observer-blind, placebo-controlled study to assess immunogenicity, efficacy and safety of BNT162b2 [mRNA] vaccine. The available study results showed that BNT162b2 [mRNA] vaccine at 30µg administered as a 2-dose schedule (21 days apart) achieved a short term efficacy of 95% against COVID-19 in individuals ≥ 16 years of age who did not have prior SARS-CoV-2 infection. The safety analysis in approximately 38,000 participants who had a median of 2 months follow up post 2nd dose revealed mild or moderate reactogenicity, low incidence of serious adverse events, and no clinically significant safety concern.

Limitations of the current data include:

- Safety follow up is currently limited to median two months post Dose 2.
- The duration of immune response and vaccine protection is not currently known.
- Vaccine efficacy against asymptomatic infection and viral transmission are not yet known.
- The data in immunocompromised individuals are very limited.
- Lack of data in paediatric subjects, pregnant women, and lactating mothers.

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

Delegate's preliminary view

The Delegate has no reason to say, at this time [11 January 2021], that the application for Comirnaty should not be approved for provisional registration.

The indication revised by the sponsor following TGA request is considered acceptable by the Delegate.

The final decision, including Conditions for Provisional Registration, will be made following the ACV discussion.

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

1. Based on the evidence at this point in time, can the ACV advise whether the benefits-risks balance is positive for the use of COMIRNATY COVID-19 Vaccine in individuals 16 years and older in the Australian context to support the provisional registration?
2. Can the ACV comment on the indication proposed by the Delegate and the indication revised by the Sponsor?
3. As the safety follow up is currently limited to a median 2 months post-Dose 2, can ACV comment on the likelihood of vaccine-related AEs occurring after more than 2 months post vaccination, particularly with the new mRNA vaccine?
4. Can the ACV comment on the proposed pharmacovigilance activities?

ACV discussion

Epidemiology

The first confirmed death from COVID-19 disease was in Wuhan, China in January 2020. There is an unmet need for safe and effective COVID-19 vaccines during the current public health emergency, declared to be a pandemic on 30 January 2020.

Australia is currently a low SARS-CoV-2 virus transmission environment, however case numbers could rise rapidly at any time. Nations that have already released the vaccine under emergency-use type arrangements have substantially higher rates of COVID-19 disease in their populations than does Australia.

Inclusion of 'pandemic' in the indication was not supported, as the vaccine's approval may outlast the pandemic designation.

International regulatory status of BNT162b2 [mRNA] COVID-19 vaccine

- MHRA (UK) issued an Emergency Use Authorization (EUA) on 2 December 2020
- Health Canada issued an interim authorisation on 9 December 2020
- FDA issued an Emergency Use Authorization (EUA) on 10 December 2020
- Health Sciences Authority (HSA), Singapore issued an interim authorisation on 14 December 2020
- Swissmedic granted conditional authorisation on 19 December 2020
- EMA granted conditional authorisation on 21 December 2020.

Quality

BNT162b2 [mRNA] COVID-19 vaccine is the first mRNA vaccine to be used in humans in Australia.

The vaccine comprises a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The RNA is encapsulated in lipid nanoparticles, which enables entry into host cells, expression of the S protein, and elicitation of both antibody and cellular immune responses.

Members discussed the number of doses that can be removed from each vial. The PI states 5; the FDA information linked to the vaccine labels, and official advice in Europe, advise that 6 doses can be extracted; there are reports of 7 doses obtained from single vials. The ACV recommended that the Australian position is clearly communicated, including whether any change to the FDA information linked to the vaccine labels would flow automatically to become part of official Australian advice.

EMA report notes presence of truncated/modified forms of mRNA at higher concentrations than in clinical trial. If this leads to a reduction in the full-length mRNA, the immune response may be affected.

Residual DNA should be part of batch testing; increased DNA contamination has the potential to increased reactogenicity.

Temperature monitoring throughout the supply chain is critical. It was noted the Australian Government will have a lead role in traceability and management of stock.

Efficacy

Study C4591001 is the global, Phase 1/2/3, randomised, multinational, placebo-controlled, observer-blind study, conducted in healthy individuals. The study consists of:

- Phase 1, to identify preferred vaccine candidate and dose level, and demonstrating robust SARS-CoV-2 neutralization and S1-binding IgG antibody levels in both younger and older adults as well as initial safety data
- Phase 2, of safety and immunogenicity in the first 360 participants. It was noted that some participants appeared to be non-responders.
- Phase 2/3, of efficacy and safety evaluation in a larger population (21,823 persons were in the vaccine arm and 21,828 in the placebo arm).

The C4591001 study, which is ongoing, showed vaccine efficacy that was remarkably consistent across age (median age 52 years; 42.6% >55 years), gender, race and ethnicity demographics. Vaccine efficacy was also demonstrated in those with one or more comorbidities (20.5% had any comorbidity - most frequently diabetes (8.4%) and pulmonary disease (7.8%)).

Consistent with the provisional approval pathway, and in addition to the limitations of data included in the Delegate's overview, the ACV noted:

- Protection from long-term complications secondary to SARS-CoV-2 infection, and effect on mortality, are not yet known
- Lack of data in children under 12 years (and limited data for those 12-15 years which was not reviewed in this submission), pregnant women, and lactating mothers
- No data on concurrent administration with other vaccines
- No data on mixed schedules with other potential COVID-19 vaccines
- An immunological correlate of protection is not established
- No data are available in the Aboriginal and Torres Strait Islander population
- The sponsor had not provided immunogenicity subgroup analysis by subdividing the age groups, such as 75-85 year olds
- There were few participants with renal failure as a co-morbidity, or other groups who may respond poorly to vaccines
- There are limited data to inform the duration of protection provided by this vaccine.

The ACV noted that serological testing of nucleocapsid antibodies in recipients was planned to determine vaccination efficacy against asymptomatic infection and recommended that these results be reported when available.

Safety

The ACV noted that vaccine candidate induced poly-functional and pro-inflammatory $CD4^+/CD8^+$ T cell responses. Study data shows that the cytokine profile indicates a favourable Th1 response and only a minimal Th2 immune response. The strong binding with neutralising antibody plus animal model and preliminary clinical trial data lessens concerns over the risk for vaccine-associated enhanced disease, but there is still a need to monitor for this over a longer follow-up period.

The ACV noted:

- Consistency of safety data, particularly reactogenicity data, across all trial phases
- Clinical trials were powered to detect adverse events up to a rate of approximately 1 in 5000 persons.
- In the reactogenicity cohort (n=8,183 subjects) most local adverse events (AEs) were mild or moderate and few severe local reactions were reported after either dose. Pain

at the injection site was reported more frequently in the younger age group than the older group with a similar frequency after dose 1 and 2. Frequencies of injection site redness and swelling were similar across age groups after both doses.

- Systemic AE in the reactogenicity cohort, such as fever, chills, fatigue, headache and muscle and joint pain after Dose 2 were generally higher in frequency than after Dose 1 across age groups, and occurred at a lower frequency in those >55 years compared with younger subjects.
- Median duration of either fever or chills from first to last day after Dose 1 and Dose 2 was 1 day
- Patients who had had COVID-19 previously experienced same or fewer AEs (noting small numbers)
- In the total safety cohort (n=37,586) there were no reports of transverse myelitis or Guillain Barre Syndrome in clinical trials, but there was a numerical difference in the incidence of Bell's Palsy (4 in the vaccine group vs 0 in the control group). There were no reports of central nervous system AEs such as ADEM. There was no report of anaphylaxis.

The ACV noted the TGA is waiting on further data concerning whether polyethylene glycol (PEG) in the vaccine may be the cause of reports of the anaphylaxis described from post-vaccine implementation experience from overseas, particularly in the United States, at a rate of approximately 1 in 100,000 recipients (noting most were healthcare workers and many had pre-existing allergies to a number of antigens, e.g. insect sting, foods etc). It was noted that the risk of allergic reactions may be related to the molecular weight of the PEG component. It was also noted that polysorbate 80, a related ingredient, is used in multiple vaccines in Australia but there has been minimal reporting of anaphylaxis.

It was noted a known allergy to any component in the vaccine, including PEG, is a contraindication for use of the vaccine. ACV also noted clinical guidance should emphasise the importance of being able to manage anaphylaxis, and that, in the USA it is recommended to observe patients with a history of anaphylaxis to any allergen for at least 30 minutes after vaccination.

The ACV noted that pregnant women are not included in any study. The ACV also noted nonclinical studies do not suggest direct or indirect harmful effects with regard to fertility, embryo-fetal development or post-natal development. The reports of supernumerary lumbar ribs are of uncertain clinical relevance to humans and may reflect different reporting in historical controls. Following additional information from the sponsor, the TGA evaluators now agreed with the sponsor's proposal of Use in Pregnancy Category B1. It was felt there are no significant concerns for the use of this vaccine in breastfeeding women.

The ACV noted the use overseas of shared clinical decision-making tools to aid pregnant woman in decision-making on vaccine administration. The ACV also noted the need for up-to-date information on contraindications, efficacy and safety to be made available to consumers as it becomes available to facilitate informed decision making.

Consistent with the provisional approval pathway, limitations of data include:

- No studies of complement activation and cytokine stimulation.
- Safety concerns to be addressed in ongoing and planned pharmacovigilance activities:
  - Anaphylaxis
  - Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

- Use in patients with co-morbidities, including frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
- Use in immunocompromised patients, and patients with autoimmune or inflammatory disorders
- Use in pregnancy and while breast feeding
- Interaction with other vaccines
- Long term safety data.

Risk Management Plan

The sponsor has proposed 11 studies to be undertaken as part of provisional approval pathway: 6 interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, one study in high risk adults and one study for vaccine interactions) and 5 non-interventional studies (4 safety and one effectiveness).

C4591001 and C4591011 are underway. The protocol for the co-administration study may not be available until September 2021, which should be accelerated if possible.

Conditions of provisional registration will include that the sponsor submit safety analysis at 6 months post Dose 2 from Study C4591001 (Phase 2/3). There will also be expedited monthly, safety summary reports (including safety data for patients in Australia) for the first 6 months post registration. The vaccine will be included in the Black Triangle Scheme.

The ACV noted an overview of the AusVaxSafety active vaccine surveillance program intended to be put in place for COVID-19 vaccines; further information will be shared with the sponsor outside of these ACV minutes.

The ACV noted an overview of enhancements to spontaneous surveillance by the TGA intended to be put in place for COVID-19 vaccines. The ACV noted that surveillance systems need to ensure capture of AEFIs in all settings where vaccines may be administered (e.g. aged care, workplace programs).

The ACV noted the importance of determining the background rate of syndromes and diseases that may be regarded as potential adverse events given the likely widespread use of this vaccine.

Examination of background rates of AESI (e.g. Bell's Palsy) should be conducted using appropriate datasets, noting some conditions may be more likely managed in primary care than in hospital settings.

The ACV also noted the need for inclusion in the Product Information of clinical advice to be provided for individuals with specific conditions (e.g. pregnancy, history of anaphylaxis) or for those in which clinical trial data are limited, such as those with immunocompromise, autoimmune disease or the frail elderly.

In addition to the Product Information, the ACV also noted the need for assessment and advice for those who experience an adverse event following immunisation, or where there are deviations from administration protocols (e.g. inadvertent use of vaccine not stored appropriately, expired vaccines, missed second doses).

Adverse Events of Special Interest (AESI)

The ACV particularly noted the following AESI.

Lymphadenopathy: in the BNT162b2 group, 64 participants (0.3%) reported an AE of lymphadenopathy (54 in the younger age group and 10 in the older age group), and 6 in the placebo group. The mean duration was 10 days, with 12 events were ongoing at the

time of the data cut-off date. The ACV commented that these reports were not unexpected given the strong immune response to the vaccine, including in lymphoid immune sites. In addition, recorded cases were not severe, with the exception of one patient who had other health conditions.

Hypersensitivity: in the USA, if patients have a history of serious allergy and/or carry an adrenaline (epinephrine) auto-injector, the patient is monitored for 30 minutes instead of 15 minutes post-vaccination. In the US, contraindications include persons who have had immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG).

The ACV noted the challenge in assessing the mechanisms of early onset severe allergic events, for example, the Brighton Collaboration definition will not differentiate between IgE-mediated reactions and CARPA (complement activation-related pseudo-allergy).

Anaphylaxis: no case was observed in study participants. However, there have been recorded cases of anaphylaxis in post market surveillance (11.1 cases per million doses, mostly in healthcare workers).

Facial paralysis: there were 4 reports of facial paralysis (Bell's Palsy) in the vaccine group with none in the placebo group. Based on background rates, the observed reports are within the expected range. It is noted that Bell's Palsy may not be documented in hospital-inpatient based surveillance, and emergency department or primary care surveillance may be required.

Vaccine errors: Possible contributions from: mixing errors or omissions with a two-component vaccine; miscommunications (exacerbated by personal protective equipment); mass immunisation including use of multi-dose vials (inexperienced staff; changes to usual protocols, technology and documentation); temperature excursions.

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, can the ACV advise whether the benefits-risks balance is positive for the use of Comirnaty COVID-19 vaccine in individuals 16 years and older in the Australian context to support the provisional registration?**

The ACV advised that the efficacy and safety data were sufficient to support provisional registration of Comirnaty COVID-19 vaccine in individuals 16 years and older in the Australian context.

There is limited or no information regarding patients with autoimmune or inflammatory disorders, immunocompromised individuals, pregnant women and individuals with *a history of* anaphylaxis. Clinical guidance will be required to assist individuals *with* decision making.

2. **Can the ACV comment on the indication proposed by the Delegate and the indication revised by the Sponsor?**

The ACV supported the changes in product indication revised by the sponsor. The ACV recommended to remove the condition 'in an officially declared pandemic' from the indication and agreed on Comirnaty (BNT162b2 [mRNA]) COVID-19 vaccine has provisional approval for the indication below:

> Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 16 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.

3. As the safety follow up is currently limited to a median 2 months post-Dose 2, can ACV comment on the likelihood of vaccine-related adverse events occurring after more than 2 months post vaccination, particularly with the new mRNA vaccine?

The ACV advised that it is unlikely for vaccine-related adverse events to occur more than 2 months after vaccination based on available data. However, there is limited information on the use of mRNA vaccine in humans, which underpins the need for post market vaccine safety surveillance.

4. Can the ACV comment on the proposed pharmacovigilance activities?

The ACV advised that the RMP is suitable with the addition of:

- earlier conduct of co-administration study during the 2021 southern hemisphere influenza vaccinations
- vaccination errors should be reported, whether they resulted in adverse event or not
  - there should be a systematic method to include and categorise error reports
  - include *an* error surrogate as AESI- e.g. SIRVA[2]
- AESI surveillance plan should address
  - standard definitions
  - background rates are critical for analysis and communication
  - for some AESI, general practice datasets may provide more data than hospital databases (e.g. Bell's Palsy)
- Surveillance should include all settings in which vaccine may be delivered including aged care.

5. Other advice

Regarding the Product Information, the ACV advised[3]

- 'Do not shake' is critical to correct reconstitution of the vaccine. This warning needs prominence. As this is a change to common clinical practices, supportive education by other means is also needed.
- Reiterate the importance of batch recording in the Australian Immunisation Register.
- *The minimum* 15 minute observation period following administration should be mandatory, not merely recommended.

Regarding the label, the ACV advised

- The expected labels refer to the FDA fact sheet, which currently permit the extraction of 6 doses from the vial of reconstituted vaccine, compared to the 5 doses stated on the label itself.

[2] https://www.tga.gov.au/committee-meeting-info/acv-meeting-statement-meeting-11-5-december-2018

[3] 'Reconsideration of the deletion of the advice that protection commences about 7 days post-Dose 2. Such information is important to flow-through to the CMI.' was included in the Resolution provided to the sponsor on 15 January 2021. It was later realised that the text had been relocated rather than deleted from the Product Information.

- The Australian position will need to be clearly communicated.

Regarding the Consumer Medicine Information, the ACV advised *consideration be given to the following:*

- Relevant consumer information, whether as a CMI or in other information formats, will be critical to informed consent in a campaign roll-out.
- Consumer information should be frequently updated as information matures. Consideration is required on how to 'push' updated information to consumers.
- Provision of information *on* the impact of deferring or not having the second dose.
- How and when to provide to consumers with information, especially regarding pregnancy.

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 16 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 6pm on 19 January 2021

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au