# CLINICAL EVALUATION

## Comirnaty
## (COVID-19 mRNA Vaccine)

## Applicant: Pfizer/BioNTech

Based on Final Analysis Interim Report - data cutoff: 14 November 2020

| | |
|---|---|
| **TT Number** | TT50-10853 |
| **Application ID** | 109400 |
| **Date received:** | 13 November 2020 |
| **Date of this report:** | January 2021 |
| **Evaluator** | s 9(2)(g)(ii) |
| **Reviewer** | s 9(2)(g)(ii) |

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**Limited glossary**

| | |
|---|---|
| ACV | TGA's Advisory Committee on Vaccines |
| CEF | MHC-class I restricted peptides originating from CMV, EBV, and flu (influenza) virus |
| CEFT | MHC-class II restricted peptides originating from CMV, EBV, Flu (influenza) virus and tetanus toxin |

| | |
|---|---|
| CoV | coronavirus |
| COVID-19 | coronavirus disease 2019 |
| CSR | clinical study report |
| EUA | (FDA's) Emergency Use Authorization |
| FACS | fluorescence-activated cell sorting |
| HCS | Convalescent human serum |
| IA | interim analysis |
| IRC | internal review committee |
| IRR | illness rate ratio |
| IWR | interactive Web-based response |
| LNP | lipid nanoparticle |
| MERS | Middle East respiratory syndrome |
| modRNA | nucleoside-modified messenger ribonucleic acid |
| NAAT | nucleic acid amplification test |
| N-binding | SARS-CoV-2 nucleoprotein binding |
| NT50 | neutralizing titer 50 |
| NT90 | neutralizing titer 90 |
| NVA | nonvaccine antigen |
| P2 S | SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein |
| P/B | Dose 1/Dose 2: a dosing regimen, comprising a priming immunization (dose 1) and a dose 2 immunization (dose 2) |
| PBMCs | peripheral blood mononuclear cells |
| RBD | receptor-binding domain |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SIRVA | shoulder injury related to vaccine administration |
| SRC | Safety Review Committee |
| Tdap | diphtheria vaccine toxoid; pertussis vaccine acellular 3 component; tetanus vaccine toxoid |



# SUMMARY REPORT

## I. INTRODUCTION

Pfizer have submitted a new medicine application, received 13 November 2021 (ID 109400), for a nucleoside modified messenger RNA (modRNA) vaccine: the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2 30 µg): Comirnaty (COVID-19 mRNA Vaccine).

Comirnaty (30 μg), is administered intramuscularly (IM) as a series of two 30-μg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single dose followed by a second dose 21 days later.

The proposed indication is as follows.

> COMIRNATY is indicated for 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.
>
> *Evaluator's comment*
>
> *The TGA's Delegate's Overview shows that the 'Indication revised by Sponsor following TGA request' is as follows:*
>
> > 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.

This vaccine encodes P2 S (V9), expresses a prefusion stabilized full-length variant of the SARS-CoV-2 S-glycoprotein.

The RNA-based vaccine is formulated in lipid nanoparticles (LNPs) and includes two novel lipid excipients.

| | |
|---|---|
| Proprietary Name of Drug Product | To be determined |
| Non-proprietary or Common Name of Drug Product | COVID-19 Vaccine |
| Compound Name | BioNTech code number BNT162b2 |
| Dosage Form(s) | Liquid Concentrated Formulation in a 2 mL vial |
| Strength(s) | 225 μg/vial |
| Route of Administration | Intramuscular injection |

*Formulation*

The vaccine candidate will be released as a concentrated multi-dose liquid formulation stored frozen at -90 to -60 ° C in a 2 mL Type 1 glass vial to be thawed and subsequently diluted with sterile 0.9% sodium chloride Solution for Injection, USP (saline diluent), and stored at 2-8 ° C until administration.

*Dose and administration*

The vaccine will be administered intramuscularly (IM) in the upper arm (deltoid muscle) as a series of two 30 μg doses of the diluted vaccine solution (0.3 mL each) according to the following schedule: a single 0.3 mL dose followed by a second 0.3 mL dose 21 days later (prime/boost regimen).

The draft datasheet includes, among other details, that the vaccine comes as concentrated suspension for injection for 5 doses in a 2 mL clear vial.

Store in a freezer at -90 °C to -60 °C. After thawing, the vaccine should be diluted and used immediately. After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours.

*Evaluator's comment*

*The above instructions, and details from the datasheet, will be compared against those in the IP manual when this becomes available.*

*Data cutoff*

This report is regarding the final analysis interim report - 14 November 2020 data cutoff [the 2,033 page report is dated "04-Dec-2020" in the margin]. This is the same data cutoff as data found in Emergency Use Authorization (EUA) report.

s 9(2)(b)(ii) [redacted]

s 9(2)(b)(ii)

[redacted]

s 9(2)(b)(ii)

[redacted]



## IV.5 Evaluator's overall conclusions on clinical efficacy

With currently available data from the pivotal study, follow-up data is only available for about one to two months. Therefore there is uncertainty about how long protection will last. In addition, the number of cases of symptomatic COVID-19 in subgroups of the study population is often low. There is thus uncertainty regarding efficacy in people of Polynesian and Asian ethnicity.

The pivotal study for this application is the Phase 2/3 Study C4591001 is ongoing in the USA, Argentina, Brazil, Germany, South Africa, and Turkey with the first subject first visit on 29 April 2020.

Study participants had median age 52 ears, with about 22% 65 years of age or older. There were 76 participants (0.2%) of Native Hawaiian or other Pacific Islander ethnicity. There were 1,625 participants of Asian ethnicity. At baseline, about 21% of participants had any Charlson comorbidity (including diabetes 8% and chronic pulmonary disease 8%). At baseline, 197 subjects (0.5%) had HIV infection.

The pivotal study shows two doses the modRNA COVID-19 Vaccine (BNT162b2 30 µg) three weeks apart provide 95% protection against symptomatic COVID-19 (as at data cutoff 14 November 2020, n≈ 37,000 with follow-up usually about one to two months).

At the earliest, it is from April 2021 that updated efficacy estimates regarding longer duration of vaccine protection are expected to become available.

For participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, from 7 days after the second dose, there were the following cases of symptomatic laboratory-confirmed COVID-19 of any severity;

- 8 (out of 18,198; 0.04%) in the BNT162b2 group and
- 162 (out of 18,325; 0.9%) in the placebo group.

In the placebo group, 162 instances of symptomatic COVID infection in about 2,222 person-years. Given the approximately 18,000 subjects who received placebo, surveillance time for the majority of subjects is likely to be between one to two months.

For the other co-primary efficacy endpoint, VE against confirmed COVID-19 in participants with or without evidence of SARS-CoV-2 infection was 94.6% (with 9 and 169 cases in the BNT162b2 and placebo groups respectively). In the elderly, participants ≥65 years of age with or without prior evidence of SARS-CoV-2 infection, VE was 94.7% (corresponding to 1 case in the BNT162b2 and 19 in the placebo groups).

'Severe' confirmed COVID-19 meant that subject had in addition to the confirmed Covid-19 (for example) at least; severe systemic illness (eg RR ≥30 breaths per minute); or needing high-flow oxygen, or admission to an ICU; or death. Severe disease was noted in one case of the vaccinated group and 3 cases in the placebo group. Although at this stage of the study's follow-up, only about 1% of placebo subjects have developed symptomatic COVID-19, severe disease was not common (about 2% of those with symptomatic disease had severe disease; 3 out of 162).

Some subjects who at baseline had evidence of prior COVID-19 infection, subsequently developed symptomatic COVID-19 at least 7 days after Dose 2. As noted in the VRBPAC Briefing Document, only 3% of participants had evidence of prior infection at study enrolment. These data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

## V. s 9(2)(b)(ii)




Pages 49- 69 withheld under section 9(2)(b)(ii) of the Act.

s 9(2)(b)(ii)

[redacted]

## V.8 Post marketing experience/Norway deaths

There are reports of deaths of 23 frail elderly patients shortly after receiving the Pfizer BioNTec vaccine. The Norwegian Medicines Agency (NOMA) has commented that there is no certain connection between these deaths and the vaccine.

The agency has investigated 13 of the deaths so far and concluded that common adverse reactions of mRNA vaccines, such as fever, nausea, and diarrhoea, may have contributed to fatal outcomes in some of the frail patients. "There is a possibility that these common adverse reactions, that are not dangerous in fitter, younger patients and are not unusual with vaccines, may aggravate underlying disease in the elderly".

Norwegian Authorities have prioritized the immunization of residents in Nursing Homes, most of whom are very elderly with underlying medical conditions and some which are terminally ill. NOMA confirms the number of incidents so far is not alarming, and in line with expectations.

All reported deaths will be thoroughly evaluated by NOMA to determine if these incidents are related to the vaccine. The Norwegian government will also consider adjusting their vaccination instructions to take the patients' health into more consideration.

*https://www.bmj.com/content/372/bmj.n149*

News. Covid-19: Norway investigates 23 deaths in frail elderly patients after vaccination

BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n149 (Published 15 January 2021)Cite this as: BMJ 2021;372:n149

## V.9 Evaluator's overall conclusions on clinical safety

In the Phase 2/3 Study C4591001 subjects were randomised to receive the modRNA COVID-19 Vaccine (BNT162b2 30 µg) three weeks apart. As at data cutoff 14 November 2020, safety information is available for the 'all subjects' safety population N~38,000 with medium follow-up of two months. The safety population with at least 2 months of follow-up after dose 2 had n = 19,067.

The vaccine is reactogenic, which is evident especially through information from the Phase 2/3 reactogenicity subset (using e-diary reporting). As per the CHMP assessment report summary: "Regarding reactogenicity, the most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequency of headache, fatigue and fever was higher after Dose 2 in both age groups."

For participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as AEs. AEs judged to be related to vaccination were noted in 21% of BNT162b recipients vs 5% in the placebo group. This includes injection site pain (7%), pyrexia (4%), as well as chills, fatigue, headache, and myalgia at lesser levels.

AEs were usually reported at a higher level in the younger (18-55 Years of Age) age group than in the older (65-85 Years of Age) age group. For example, 31% of this younger age group had moderate pain after the first dose, and 27% after the second dose. Systemic symptoms were common especially following the second dose (eg fatigue, headache, muscle pain and joint pain). Fever of ≥38.0° C after the second dose was noted in the younger group by 15.8%, and of ≥38.0° C to 38.4° C by 9.2%.

However, severe AEs were reported in 1.2% of the vaccine group compared to 0.6% of the (saline) placebo group, and AEs leading to withdrawal 0.2% vs 0.1%.

Uncommonly reported was lymphadenopathy in the arm and neck region (0.5% in the younger group). This was reported within 2 to 4 days after vaccination, and sometimes was slow to resolve. In addition, one subject reported angioedema 13 days after Dose 1 affecting both eyes, and another subject report hypersensitivity (allergy attack).

There was an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group).

## VI. BENEFIT RISK ASSESSMENT

*Covid-19 pandemic*

In early 2021 it is becoming clear that the novel coronavirus SARS-CoV-2 constitutes an important health hazard, especially for the elderly as well as people with comorbidities. Even relatively low mortality rates associated with the resulting disease, COVID-19, may have a substantial impact as the whole population is assumed to be susceptibility. There have now been months of waves of increased transmission and disease. In addition to the immediate sickness, a relevant proportion of patients suffer longer term adverse consequences; including eg respiratory and cardiovascular system impairment, as well as long-Covid syndrome.

*Medical need*

Public health measures have been shown to be potentially very effective, although such measures can be socially disruptive and can have large economic consequences.

Treatment of acute Covid-19 disease has improved, and several medicines are recognised to have a role in treatment.

*Populations for benefit risk assessment*

The probability of exposure to the virus, as well as the mortality and morbidity burden associated with the disease is relevant to the benefit risk. Arguably, the following populations could be considered for separate benefit risk assessments.

- The benefit risk balance of a COVID-19 Vaccine as a travel vaccine for the elderly would likely be positive for many vaccines with reasonable efficacy and safety, as globally the virus is now endemic and chance of exposure is high.
- For New Zealand residents, staff at quarantine facilities, as well as Air New Zealand staff working on international routes and healthcare professionals, are at increased risk of contact with the virus.
- As long as public health measures continue to be effective, vaccination of New Zealanders generally could become relevant when vaccine supplies allow for the entire New Zealand resident high-risk population to be covered.

*Vaccine characteristics*

The vaccine's preservative free multiple dose presentation, with need for administration close to low-temperature storage, will likely result in use in group-settings rather than episodic individual use setting (such as relevant for a travel-vaccine). Given the LNP-mRNA vaccine innovative technology, particular care in the evaluation of safety (including longer-term safety) is important.

*Benefit*

The randomised Phase 2/3 Study C4591001 shows that for participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, from 7 days after the second dose, there were the following cases of symptomatic laboratory-confirmed COVID-19 of any severity:

- 8 (out of 18,198; 0.04%) in the BNT162b2 group and
- 162 (out of 18,325; 0.9%) in the placebo group.

With currently available data from the pivotal study, follow-up data is only available for about one to two months. Therefore there is uncertainty about how long protection will last. At the earliest, updated efficacy estimates regarding longer duration of vaccine protection are expected to become available from April 2021.

In addition, the number of cases of symptomatic COVID-19 in subgroups of the study population is often low. There is thus uncertainty regarding efficacy in people of Polynesian and Asian ethnicity.

Severe disease was noted in one case of the vaccinated group and 3 cases in the placebo group; an estimated efficacy against severe COVID-19 occurring at least 7 days after dose 2 was 66.4% (95% CI: -124.8%; 96.3%).

*Risk*

The vaccine is reactogenic, which is shown especially through information from the Phase 2/3 reactogenicity subset (using e-diary reporting), for example: injection site pain (> 80%), myalgia and chills (> 30%), and pyrexia and injection site swelling (> 10%) are very common. There are lesser rates when reporting of AEs is considered, for example general disorders and administration site conditions (12% BNT162b2 vs 3% placebo). In general, AEs judged to be related to vaccination were noted in 21% of BNT162b recipients vs 5% in the placebo group - AEs includes injection site pain (7%), pyrexia (4%), as well as chills, fatigue, headache, and myalgia at lesser levels. Severe AEs were reported in 1.2% of the vaccine group compared to 0.6% of the (saline) placebo group, and AEs leading to withdrawal 0.2% vs 0.1%. Longer-term safety data is lacking.

AEs were usually reported at a higher level in the younger (18-55 Years of Age) age group than in the older (65-85 Years of Age) age group. For example, 31% of this younger age group had moderate pain after the first dose, and 27% after the second dose. Systemic symptoms were common especially following the second dose. Fever of $\geq$38.0° C after the second dose was noted by about 16% in the younger group.

**Uncertainties**

Pivotal trial design and sample size means that study results are not expected to address all of the following uncertainties.

- It is not clear that the method of administration of the Comirnaty vaccine, as described in the datasheet's 'Special precautions for disposal and other handling' section, is similar to the method of administration in the pivotal study.
- The duration of vaccine protection has not been established beyond two months.
- At this stage, there is limited evidence of protection against severe disease.

- There is no long-term safety follow-up information.
- Vaccine prevention of asymptomatic infection and disease transmission has not been established.

At this stage there is no information regarding vaccine effectiveness regarding:

- new variant virus lineages that may become important epidemiologically (including the possibility of change because of vaccine-selection pressures)
- immunocompromised people, and for pregnant women
- Pacific and Asian populations
- subjects with evidence of prior COVID-19 infection at baseline.

*Summary*

The benefit risk balance of Comirnaty (COVID-19 mRNA Vaccine) for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older, is not clear. At this stage, there is evidence only for short-term protection, and longer-term safety data are lacking. However, experience with the vaccine is accumulating rapidly.

Notwithstanding uncertainties, in the light of high clinical need and the expectation of further data (including regarding duration of protection) around April 2021, a provisional consent under section 23 of the Medicines Act 1981 may be appropriate.

## VII. PRODUCT INFORMATION

If considered for provisional consent, the datasheet will have to explain that approval was based on short-term vaccine-protection information, and that further information is expected.

Among others, issues covered in the datasheet include the following.

*The study programme did not cover pregnant women and children.*

**Pregnancy**

There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development (see Section 5.3 Preclinical safety data).

Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

*Evaluator's comment*

s 6(b)(ii) [redacted] *It is often advantageous for the New Zealand datasheet to be similar to the information for prescribers in Australia, and updating the pregnancy information in the proposed New Zealand datasheet to be similar to that for Australia should be considered.*

*IM administration*

**Thrombocytopenia and coagulation disorders**

As with other intramuscular injections, COMIRNATY should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any

coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

*Hypersensitivity*

**4.4 Special warnings and precautions for use**

**General recommendations**

***Hypersensitivity and anaphylaxis***

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of COMIRNATY.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of COMIRNATY should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.

*Evaluator's comment*

*For justification of the above general recommendation, see the section in the Safety part of this report regarding the MHRA notification of two allergic reaction events in UK December 2020.*

## VIII. RECOMMENDATION

The application is to be referred to the MAAC for final recommendation on provisional consent, as well as the proposed conditions.

## IX. SELECTED INITIAL ADVISORY GROUP COMMENTS

Responses to an early request (with very limited information) for advice from the Medsafe COVID-19 Vaccine Advisory Committee have included the following.

Covid-19 vaccines can be expected not to provide long term protection – the need for booster doses can be expected. (For viral vectored vaccines, heterologous boosting may be needed).

Significant delayed adverse consequences of vaccination, generally, are very uncommon. For example, a recent article highlighted vaccines that had been withdrawn for safety concerns. All of the events, resulting in withdrawal, occurred within 2 months of vaccine receipt (Reid S Vaccine Safety NZMJ 21 February 2020 Vol 133 No 1510. www.nzma.org.nz/journal-articles/vaccine-safety). Possible delayed AEs could include:

- VAERD in specific age groups (eg geriatric, pediatric) or in individuals with uncommon comorbidities (eg autoimmunity / immune deficiency)
- Guillain Barre Syndrome
- narcolepsy.

s 9(2)(b)(ii)

[redacted]

Pages 75- 77 withheld under section 9(2)(b)(ii) of the Act.

s 9(2)(b)(ii)

[redacted]



## II. SUMMARY

*Comirnaty COVID-19 mRNA vaccine*

This application concerns the Pfizer-BioNTech nucleoside modified messenger RNA vaccine, Comirnaty COVID-19 mRNA vaccine that is administered as two intramuscularly injected doses, 21 days apart. This innovative lipid nanoparticle RNA-based vaccine includes two novel lipid excipients. Administration is made more challenging by its availability as a concentrated multi-dose liquid formulation stored frozen at -90 to -60 ° C.

**Analysis of condition and current treatment options**

Although treatments have improved, COVID-19 causes substantial morbidity and mortality in a susceptible population. Vaccination can mitigate the impact of COVID-19.

**Benefits**

The pivotal study shows two doses the Comirnaty COVID-19 mRNA vaccine (BNT162b2 30 µg) three weeks apart to provide a high level (95%) of protection against symptomatic COVID-19 (as at data cutoff 14 November 2020, n≈ 37,000 with follow-up usually about one to two months).

*Uncertainty*

There is uncertainty regarding the duration of protection. In addition, it is not known whether vaccinated people can become infected asymptomatically and whether they can transmit the virus. At this stage, it is not known whether the vaccine protects against severe disease, and whether it would provide protection for subgroups (such as, for example, the elderly).

The Sponsor, in response to the Request for Information, noted that efficacy data is expected in 2021.

- Q1 2021; initial results regarding the possibility of asymptomatic infection in the vaccinated group.
- First half of 2021; Information regarding vaccine failure in patients given 2 doses of vaccine.
- Q3 2021; immunogenicity data for a subset of participants.
- Q3-4 2021; information regarding duration of vaccine protection.

If considered for provisional consent, the datasheet could (as is not uncommon) harmonise with the TGA approved product information and have an indication that explains that approval was based on short-term vaccine-protection information, and that further information is expected.

**Risks**

In the study programme, safety of the Comirnaty COVID-19 mRNA vaccine was similar to that of IM administered vaccines.

*Uncertainty*

While there is uncertainty regarding the unlikely possibility of rare or delayed AEs, there is increasing assurance of the safety of the Comirnaty COVID-19 mRNA vaccine with rapidly increasing international experience. Monthly periodic safety update reports will be expected for the first 6 months post approval.

## II.1 Advice sought

In its consideration of this application, the Medicines Assessment Advisory Committee (MAAC) is asked to advise whether:

– The proposed conditions for the provisional consent are appropriate.

- The benefit risk balance of the Comirnaty COVID-19 mRNA vaccine for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older is positive.
- Whether to accept the proposed indications, or to request that the Sponsor update the New Zealand datasheet so that it is harmonised with the TGA approved product information, and includes the following indication:

  Comirnaty (BNT162b2 (mRNA)) COVID-19 vaccine has **provisional consent** 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.

## II.2 Proposed conditions of provisional consent

- The sponsor must provide regular updates on the duration of efficacy and the requirement for booster doses. This should include the six months analysis data from Study C4591001. Interim report due: April 2021.
- The sponsor must provide updates on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, when these become available.
- The sponsor must submit the final Clinical Study Reports for Study C4591001 and Study BNT162-01. Due date: December 2023.
- (Monthly safety updates for the first six months following approval are covered through the RMP.)

Document 2

SCIENCE & TECHNICAL ADVISORY | RŌPŪ TOHUTOHU I TE PŪTAIAO ME TE HANGARAU

MINISTRY OF HEALTH
MANATŪ HAUORA

# Request for Information (RfI)

This form contains the details relevant to the questions posed to the Science and Technical Advisory (STA) team. The STA will respond to the request using this form which will also be stored in the STA content management system for future reference.

This form, or parts of it, may also be forwarded to other relevant parties as appropriate.

| | | | |
|---|---|---|---|
| Title | Implications of UK variant for vaccine assessment | | |
| Subject | Summary – evidence of increased transmissibility of UK variant | | |
| Reference No. | 133 | Date Received | 15/01/2021 |
| Requestor | Chris James (Medsafe), s 9(2)(g)(ii) [redacted] | Date Due | 20/01/2021 |
| Advisor | s 9(2)(g)(ii) [redacted] | Date Completed | 20/01/2021 |
| Reviewed by | s 9(2)(g)(ii) [redacted] | | |
| Information issued to | | | |
| Approved by | | | |
| Deliverables | Evidence summary | | |
| Request Outline | **Background/Context**<br>Chris James from Medsafe has been informed of an increasing risk of COVID community spread since before Christmas due to new variants, and that there has been an increase in transmission in other countries due to new variants. There are concerns over what this means for New Zealand.<br>The evidence of increased transmissibility needs to be documented, as this helps Medsafe with benefit risk consideration of the vaccine – i.e. has the benefit risk consideration changed, and is a decision based on earlier data justified?<br><br>Recommendations for vaccine roll out etc are not required, and it doesn't need to be a comprehensive literature search.<br>**Questions**<br>What is the evidence that new variants of concern, such as the UK variant, have increased transmissibility?<br>**Intended application of advice**<br>This advice will accompany Medsafe's assessment report that will go to the Medicines Assessment Advisory Committee. | | |

**Timeline**

Timeframes are extremely tight. Hence Medsafe needs this by 20 January. A delay may result in a delay on regulatory decision making as this advice will accompany the assessment report that will go to the Medicines Assessment Advisory Committee.

# Evidence summary: transmissibility of SARS-CoV-2, particularly new Variants of Concern (VOC)

## Introduction

All viruses constantly change through mutation, and therefore the emergence of new variants is expected (1). Some mutations do not confer a direct benefit to the virus, some may be detrimental, and some may confer an advantage (2). New variants may emerge and disappear, or they may persist (3). Most mutations won't significantly impact viral spread, but some mutations or combinations of mutations may give viruses a selective advantage (e.g. increased transmissibility due to an increase in receptor binding, or evasion of the host immune response by altering viral surface structures)(1). Many thousands of variants of SARS-CoV-2 are circulating, and most will likely have no effect on viral transmission or disease characteristics (1). Variants with potential to increase the risk to human health are considered variants of concern (VOC)(1).

Multiple variants of SARS-CoV-2 have been documented globally throughout the course of the pandemic (3), but some recent variants are causing particular alarm because of reported increases in transmissibility. Three variants of note are discussed in this paper, which appear to have emerged in the UK (lineage B.1.1.7), South Africa (501.V2) and Brazil (P.1). Lineage B.1.1.7 (UK variant) is discussed in most detail as it has more information available. Scientists are working to figure out whether new variants such as these may transmit more easily, cause more severe disease, or affect the efficacy of therapeutics or vaccines (3). Epidemiologically, it is quite difficult to distinguish contributors to more efficient spread (e.g. human behavioural factors, vs virologic factors)(4).

This evidence summary provides background information about the transmissibility of SARS-CoV-2 in general, and the UK variant in particular. It also considers potential implications.

A note on naming conventions: When a number of mutations occur together and become commonly detected, they are designated as a lineage or variant. A viral strain is typically a substantial change in the virus – the consensus is that none of the SARS-CoV-2 lineages are yet at a point where they are designated as a formal strain.



## UK variant

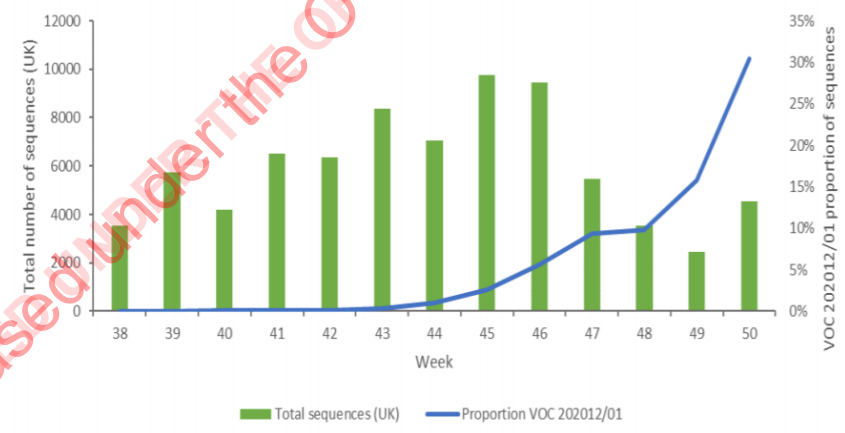
### *Origin, discovery and spread*

- In December 2020, a new variant of SARS-CoV-2 (called VOC-202012/01) was reported in the United Kingdom (5). It was designated a Variant Under Investigation on detection and re-designated as a Variant of Concern (VOC) on 18 December 2020 (6). It is also called lineage B.1.1.7. This variant was identified by the COVID-19 Genomics UK (COG-UK) consortium, which undertakes random genetic sequencing of positive samples from around the UK to help track outbreaks and identify variants (7). The authors of the COG-UK report hypothesise that the accelerated mutation accumulation in this lineage may have resulted, at least partly, from virus evolution within a chronically infected individual

(8). However, they are careful to note we cannot yet know precisely what gave rise to this lineage. Experts indicate it is likely to have evolved in the UK (7).

- The first COVID-19 case with the VOC 202012/01 variant in England was detected on 20 September 2020. Throughout December 2020, a cluster of the new variant grew rapidly, and spread to other UK locations (8). The UK experienced a rapid increase in COVID-19 case rates (with the seven-day case rate increasing from 162 cases/ 100,000 population in week 49/2020, to 344 during week 51/2020 (1). This increased case rate was especially significant in London, the South East and the East of England, and genomic analysis identified that a large proportion of sequenced cases in these areas were a new variant, VOC 202012/01 (1). The rapid increase in COVID-19 cases overall was noted to be temporally associated with the emergence of a new variant in the abovementioned areas in November 2020 (1). The B.1.1.7 lineage rapidly emerged to become the dominant SARS-CoV-2 variant circulating in England (6).
- In response to the increase in VOC 202012/01, in late December the UK announced stricter control measures to be applied, especially in affected areas in England (1)
- As of 13 December 2020, VOC 202012/02 had been identified in 1108 individuals in the UK, in nearly 60 different local authorities (7). The figure below from the ECDC risk assessment displays how the overall proportion of VOC202012/01 among all uploaded viral sequences from the UK to the GISAID database increased substantially towards the end of 2020. However, it should be noted that this data is derived from community-based sampling, and is not geographically representative, or representative of hospitalised cases (1).

**Figure 5. Fraction of UK SARS-CoV-2 sequences classified as VOC 202012/01 per week, and total sequences per week from the UK, published in GISAID EpiCoV up to 27 December 2020**




*Source: GISAID EpiCov database. Weeks 51 and 52 are omitted due to very few sequences being available for those weeks (252 and 0 respectively).*



- As of 4 January 2021, a total of 6,008 cases with this variant had been identified in England, via routine genomic surveillance, across the majority of local authorities (7). Most cases were identified in London and the East and South East of England but the variant has also been reported elsewhere, including Wales and Scotland (7).
- As of 7th Jan 2021, 45 countries had reported the presence of the B.1.1.7 variant (5), including in managed isolation in New Zealand. As of 18 January, 16 cases of the B.1.1.7 variant were reported in New Zealand.

- The B.1.1.7 variant is quickly becoming the dominant lineage across the UK, though it is unclear how much this is due to viral genetics, versus seasonal changes and social factors. As of 4 January 2021, the new variant comprises approximately 71.5% of new cases in the UK. However, the new variant may not be simply replacing the current strain, but also adding to existing variant: "Further, excess SGTF growth rates generally outweighed declines in non-SGTF positives, showing B.1.1.7/VOC202012/01 is likely adding to, rather than replacing, existing strains". (9)

### *UK variant features*

- The B.1.1.7 variant is characterised by a set of 17 mutations present across several genes (2). Many of these mutations have been identified before in varying frequencies (2), but the large number and combination of these in a variant is new (8). Several of the genetic changes occur in the spike protein (4)(8), which the virus uses to enter host cells.
- Three key genetic changes to the spike protein include a mutation at position 501, a deletion at position 69-70, and P681H. The mutation N501Y is in the receptor binding domain of the spike protein. This may be particularly significant because theoretically, changes in this part of the spike protein may make the virus more easily transmissible (7). N501Y has been associated with increased infectivity and virulence in a mouse model (4). This mutation has also been reported in South Africa, Australia, Denmark, Brazil and the US (2). H69del/V70del may be associated with immune response evasion (9). The spike protein deletion at position 69-70 also affects PCR assays targeting the S-gene by preventing probe binding and causing S-gene target failure (SGTF)(1, 9). SGTF can be used as a proxy to screen for VOC 202012/01, though whole genome sequencing is more definitive.

### *Transmissibility of the UK variant*

- Preliminary analysis in the UK indicated that this variant is significantly more transmissible than other variants – it may increase transmissibility up to 30-50%, and increase the reproductive number by 0.4 (10). (6).
- The proportion of cases tested which have the proxy S gene target failure (SGTF) – a proxy target that can be reliably used to identify VOC 202012/01 - continued to rise through December in England. In the first week of December approximately 27.7% of cases contained SGTF, rising to 71.5% in the week 29 December 2020 to 4 January 2021 (6).
- The 'secondary attack rate' (SAR) is the percentage of contacts of a case who become infected. A secondary attack analysis by Public Health England estimated that 14.7% of the contacts of a case with VOC 202012/01 become infected, compared to 11% of contacts of a wild type case (6). However, the study did not cite whether these were close or causal contacts, and it is unclear what biases may affect this data (e.g. focusing testing on areas where B.1.1.7 is common will result in higher proportions of tests with that variant).
- Other countries that prioritise genome sequencing, notably Denmark, have also seen a rapid rise in the proportion of B.1.1.7 variants in their sequencing data, which increases confidence that the lineage is in fact more transmissible, rather than it becoming more common in the UK due to other factors.
- A pre-print posted by Volz et al on 4 January examined epidemiological evidence for the lineage B.1.1.7 having a transmission advantage, through several analyses (11). All indicated that this VOC has a substantial transmission advantage. The key metric is that the $R_o$ (reproduction number) of this

VOC was 0.4-0.7 higher than previously circulating variants, which is a significant shift. The ratio of reproduction numbers varied between 1.4 and 1.8.

Volz et al also note a small but statistically significant shift towards higher rates of infection by the VOC in those under 20, compared to non VOC. However, it is possible that this is related to movement/ mixing of this cohort, rather than viral genetics.

- A pre-print posted on 27 December 2020 reported that individuals with B.1.1.7 had higher viral loads (which may result in more viral shedding from infected individuals, and may translate to higher infective doses)(4).
- Another pre-print from 15 January 20201 concluded that "direct population-representative estimates show that the B.1.1.7/VOC202012/01 SARS-CoV-2 variant leads to higher infection rates, but does not seem particularly adapted to any age group"; there was no evidence that the rates of the new variant were growing faster or slower in those under and over high school age. (9)
- Some countries have reported increases in the relative frequency of B.1.1.7, but several factors may affect reporting estimates (5). O'Toole et al (2021) note that the number of variant genome sequences reported in each countries will be influenced by the amount of local genomic surveillance, potential targeting of sequencing towards travellers from certain countries, the amount of international travel among affected countries, and the amount of local transmission (5)

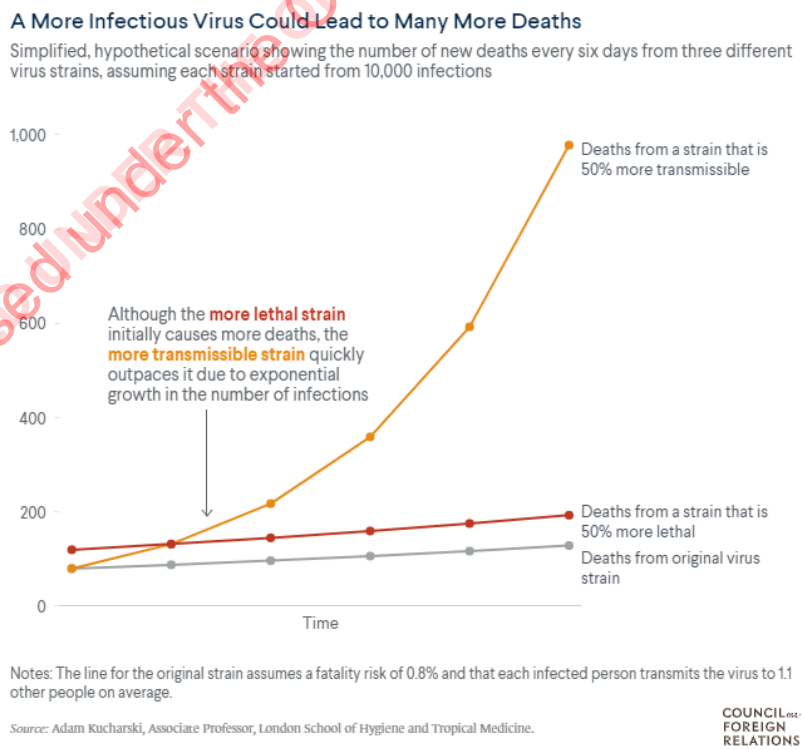
## Other variants

- On 18 December 2020, the South African government reported the emergence and rapid increase of another new variant identified through routine genomic surveillance, designated 501.V2(1). This variant also has multiple changes in the spike protein, including the same N501Y mutation present in VOC 202012/01. The South African variant (also known as 20H/501Y.V2 or B.1.351) appears to be more transmissible(12); One preprint estimates that the South African variant is 50% more transmissible than previous variants(13) similar to the increased transmissibility of the UK variant.
- The South African variant contains multiple mutations affecting the spike protein, including K417T, E484K, N501Y. One of the mutations, E484K, has the potential to reduce antibody recognition, and it may help SARS-CoV-2 to bypass immune protection provided by prior infection or vaccination.(14) As of 7 January 2021, 13 countries had reported B.1.351/501Y.V2 (5).
- In a preliminary study evaluating the effectiveness of the Pfizer/BioNTech vaccine against the N501Y mutation, found in both the UK and South African variants, researchers found no reduction in neutralizing activity against the virus with the N501Y mutation (15). However, this study did not evaluate the full set of observed spike mutations.
- A Brazilian variant (known as P.1 lineage or 20J/501Y.V3) also has multiple mutations affecting the spike protein and shares the same K417T, E484K, and N501Y spike protein mutations as the South African variant. There is evidence to suggest that some of the mutations in the P.1 variant may affect its transmissibility and antigenic profile, which may affect the ability of antibodies generated through a previous natural infection or through vaccination to recognize and neutralize the virus (16).
- A recent study reported on a cluster of cases in Manaus, the largest city in the Amazon region, in which the P.1 variant was identified in 42% of the specimens sequenced from late December. In this

region, it is estimated that approximately 75% of the population had been infected with SARS-CoV2 as of October 2020. However, since mid-December the region has observed a surge in cases. The emergence of this variant raises concerns of a potential increase in transmissibility or propensity for SARS-CoV-2 re-infection of individuals(17).

## Implications of new variants

- New variants such as the B.1.1.7 lineage are having significant implications for managing the COVID-19 pandemic world-wide, for example with increased travel bans internationally, and more elaborate testing regimens.
- The increased transmissibility would likely lead to greater number of secondary cases and hence increase the burden on contact tracing; As preliminary data suggests, the number of contacts infected is 50% higher compared to the current strain (e.g., if the index case has 100 contacts, number infected increases from, say, 12 previously to 18 with new variant).
- While there is no evidence that the UK VOC is responsible for more severe disease, the fact that it infects more people may result in a higher number of people that need medical care. This is observed in both the test positivity rates and the hospitalisation numbers out of the UK. A 'back of the envelope' calculation (below) from a mathematical epidemiologist at the London School of Hygiene and Tropical Medicine, shows that, compared to a virus that infects 10% of contacts with an 0.8% mortality rate, a variant that is 50% more transmissible leads to an increased number of daily deaths(18). Note that this is a very simple analysis for a media brief, comparing hypothetical exponential growth curves and does not take into account any other factors related to transmissibility.




- The CDC has noted that modelling suggests that lineage B.1.1.7 has the potential to increase the U.S. pandemic trajectory, warranting universal and increased compliance with mitigation strategies and suggesting that higher vaccination coverage might be needed to protect the public, i.e., the herd

immunity threshold is greater but there is no difference in the individual protection afforded by the vaccine. The CDC predicts that B.1.1.7 may well become the dominant variant in the US by April-May 2021(19).

## Conclusions

- It seems likely that the UK variant B.1.1.7 has significantly increased transmissibility. The latest evidence from Public Health England using contact tracing data, estimates that the new variant increases the number of infected contacts of the index case by 30-50%, and this is seen consistently across geographic regions in England.
- This coupled with the high rates of infection in the UK, Europe, South Africa and the USA increases the risk of new cases with this variant arriving in New Zealand.
- The UK variant is increasingly becoming the dominant variant in the UK and the US CDC predicts that it may become the dominant variant there by approximately April 2021. A small number of cases in New Zealand MIQ have been recorded so far, but this is likely to increase.
- New Zealand has imposed pre-departure testing for all long-haul returnees but this will not totally prevent cases of these variants arriving in New Zealand, although it may reduce the numbers arriving.
- Although there is emerging evidence of increased transmissibility there is no evidence on the need to change current quarantine Infection Prevention and Control procedures.
- If there is a breach from MIQ and community transmission occurs, it is likely to spread more rapidly and be more challenging to contain and also put pressure on contact tracing resources.
- As in other countries, in the setting of an outbreak rapid deployment of a vaccine should be considered to protect vulnerable groups (e.g., community clusters, vulnerable populations such as the elderly, and Maori and Pasifika communities) and potentially provide some reduction in transmission rates.

Ian G Town

***Dr Ian Town***

***Chief Science Advisor***

| | |
|---|---|
| Next Steps | Advice sent to Medsafe January 20th |

| | |
|---|---|
| In the development of this work, the following parties have been consulted with: | s 9(2)(g)(ii) [redacted] |
| What are the implications and considerations of this advice on Te Tiriti o Waitangi and equity? | Not considered in detail |

| Resources used: | | |
|---|---|---|
| Ministry of Health Policies and Procedures | ☐ Yes ☒ No | |
| External Health Scientific organisations | ☐ Yes ☒ No | |
| Existing database of RFAs | ☐ Yes ☒ No | |
| Internal MH Advice | ☒ Yes ☐ No | |
| External Expert Advice | ☐ Yes ☒ No | |
| Literature Review | ☒ Yes ☐ No | Abbreviated |

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# Memo

MINISTRY OF HEALTH
MANATŪ HAUORA

| | |
|---|---|
| **Date:** | 3 February 2021 |
| **To:** | Chris James, Minister's Delegate, Group Manager, Medsafe |
| **Copy to:** | |
| **From:** | s 9(2)(g)(ii) , Acting Manager, Product Regulation |
| **Subject:** | **Medicines Assessment Advisory Committee minutes and recommendations – 109th meeting on 2 February 2021** |
| **For your:** | Action and Decision |



**Background**
This memo asks you to consider recommendations made to you by the Medicines Assessment Advisory Committee (MAAC), in your capacity as the Minister's delegate, for the purpose of granting consent to the distribution of medicines under sections 20 and 23 of the Medicines Act 1981 (the Act).

The MAAC is a Ministerial advisory committee established under section 8 of the Act to provide advice in relation to the approval of medicines.

**Summary**
The MAAC met on **2 February 2021** to consider applications you have previously referred to it under section 22(2) of the Act.

Attached is a copy of the ratified minutes of the 109th meeting of the MAAC, which include the Committee's recommendation as to the decision you should make in relation to the medicines considered. A summary of recommendations is also provided.

**Action**
The MAAC has recommended that you grant provisional consent to the distribution of the following medicine: Comirnaty (COVID 19 mRNA vaccine) (Pfizer BioNTech) 0.5 mg/mL concentrate for injection (TT50 10853). Medsafe supports this recommendation and you are therefore asked to sign the attached letter to the applicant company to advise them of the outcome of the MAAC recommendation.

**Recommendations**
It is recommended that you:

| | | | |
|---|---|---|---|
| 1. | Note | the minutes from the 109th meeting of the MAAC held on 2 February 2021. | Yes/No |

| | | | |
|---|---|---|---|
| 2. | Sign | the attached letter to the applicant company, Pfizer New Zealand, advising them of the MAAC's recommendation that you grant provisional consent to the distribution of the medicine Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853) | Yes/No |

Signature s 9(2)(g)(ii) Date: 3 Feb 2021

s 9(2)(g)(ii)

Acting Manager, Product Regulation

Signature Date: 3/2/2021

Chris James

Group Manager, Medsafe

# Medicines Assessment Advisory Committee

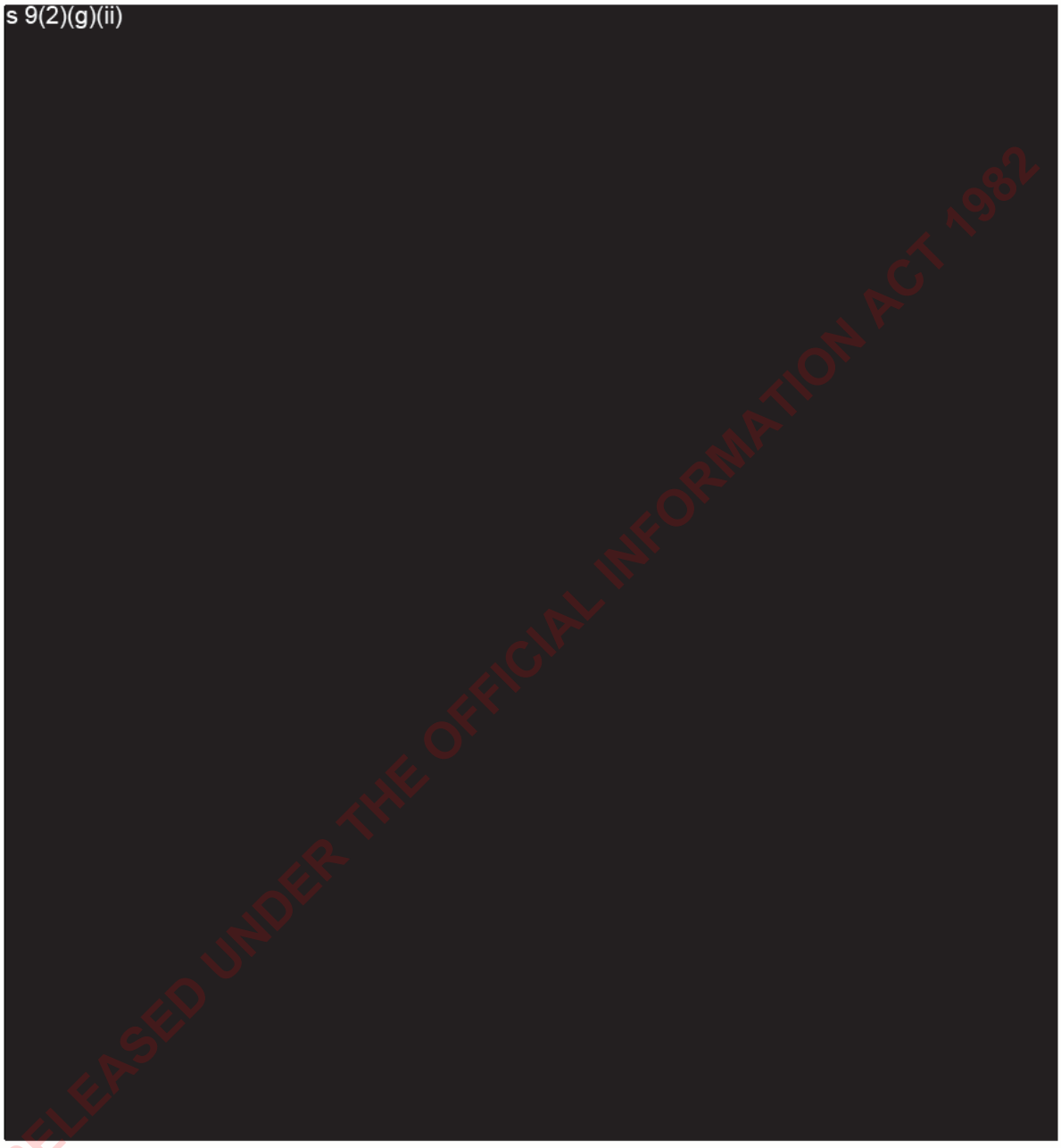


## Minutes of the 109th meeting held on Tuesday 2 February 2021

## Ministry of Health
## Wellington

# Minutes of the 109th meeting of the Medicines Assessment Advisory Committee by videoconference on 2 February 2021 at 9:30am

s 9(2)(g)(ii)





## 1 Welcome

The Chair opened the 109th meeting at 9:30am and welcomed members and guests to this extraordinary meeting to consider a recommendation on the approval of Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection submitted by Pfizer New Zealand Limited. The Committee members introduced themselves.

## 2 Apologies

Apologies were received from s 9(2)(g)(ii) [redacted] s 9(2)(g)(ii) [redacted] as unavailable over the duration of the meeting.

## 4 Declaration of conflicts of interest

Members submitted their conflicts of interest forms to the Secretary.

The following new conflicts of interest were declared:

a. s 9(2)(g)(ii) [redacted] before accessing the meeting documentation, had declared that she had shares in Pfizer, Moderna, Johnson & Johnson and Vitalis. This precluded her from accessing the meeting documentation and from attending the 109th meeting.

b. s 9(2)(g)(ii) [redacted] declared he had shares in Ergomed and BLIS Technologies

All other members declared they had no additional interests that would pose a conflict with any of the items on the agenda.

The Committee agreed that, other than s 9(2)(g)(ii) [redacted], there were no potential conflicts of interest that were considered likely to influence the discussion or decisions of the Committee at this meeting.

## 5 Applications for consent to distribute a new medicine under section 20/23 of the Medicines Act 1981 (referred by the Minister of Health under section 22(2))

### 5.1 Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853) Pfizer (NZ) Ltd

The Pfizer-BioNTech Covid-19 mRNA vaccine has been developed in response to the global pandemic of the SARS-COV-2 virus that causes Covid-19. This is the first application to market a Covid-19 vaccine in New Zealand and the first Covid-19 vaccine to be granted emergency use authorisations in the UK and the US. Australia provisionally approved this vaccine on 25 January 2021. Due to the continued global spread of the virus and its variants, availability of a vaccine is an important part of the New Zealand Government's Covid-19 strategy.

New Zealand does not have an emergency use authorisation pathway and currently does not have the public health emergency situation of many other countries, but this situation can change.

A new medicine application was submitted by Pfizer New Zealand Limited for Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853) under section 20 of the Medicines Act 1981.

The application is being considered for provisional consent under section 23 of the Medicines Act 1981 for the following indications:

> *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 the vaccine must be in accordance with official recommendations.*

The application has been submitted via an expedited rolling review process and has been assessed under urgency due to the significant clinical need for a COVID 19 vaccine with a positive benefit risk profile. The initial application was received on 13 November 2020, after which a total of eight tranches of supporting information were submitted to Medsafe. Following assessment of these data packages, a request for additional information was issued on 15 January 2021 and response from Pfizer was received on 22 January 2021. Additional responses and data to support a change in the number of deliverable doses per vial were received on 27 January 2021. All additional data has since been assessed and a final recommendation has been made on 28 January 2021.

Given the rapid development of this medicine and the urgent clinical need that exists in New Zealand, there are several aspects of the data required to support quality, safety and efficacy that are not available at the time of completion of the evaluation. It is also proposed that any provisional consent be granted for a period of nine months, before which time all additional data should be received.

It was requested that the Committee focus on the specific aspects in their consideration of the application:

- The conditions and consent time period proposed for provisional consent under section 23 of the Medicines Act 1981. Specifically, whether these are appropriate and sufficient given the data provided up to the time of referral, as well as whether any additional conditions should be applied.
- Whether the proposed indications for the medicine are appropriate and supported by the clinical data available, as well as whether any additional restrictions should be applied.

The following is the full list of evaluation reports and supporting documentation that were provided:

- Final evaluation report – Quality (includes final recommendation)
- Final evaluation report – Novel excipients
- Final evaluation report – Non-clinical
- Final evaluation report – Clinical
- Final evaluation report – RMP
- Application dossier composed of iterative rolling review tranches and RFI responses and additional data
- TGA assessment documentation

- Advice from the Ministry of Health Science and Technical Advisory Group (STAG) on new SARS-CoV-2 virus strains and the implications for COVID-19 vaccines

Pfizer New Zealand was informed of the referral on 29 January 2021.

***Medsafe Presentation***

Medsafe presented an overview of what is known about Comirnaty to the Committee.

***Pre-clinical discussion***

The Committee considered the following documentation:

- Final evaluation report Non-clinical

The Committee noted that the pre-clinical questions raised in the report were addressed satisfactorily by the company. The Committee noted that pre-clinical observations such as hepatoxicity are not apparent in the clinical data. The reactogenicity seen in the clinical data does not appear to be a concern in the pre-clinical data. The data on long terminal half-life of the lipid nanoparticles was considered unusual but unlikely to be a safety concern, as only two doses are intended to be administered. The pre-clinical data did not suggest safety concerns in pregnancy.

The Committee considers that generally the pre-clinical data has been superseded by the clinical data. The Committee had no safety concerns based on the preclinical data.

The Committee adopted the report and agreed with the conclusions.

***Evaluation***

- **Quality evaluation report (including Novel Excipients evaluation report)**

The Committee considered the following documentation:

  - Final evaluation report Quality (includes final recommendation)

The Committee noted that the Medsafe evaluation report was detailed and comprehensive. It was noted that many of the questions posed by Medsafe had been resolved and unresolved questions were included as conditions for the provisional consent.

The number of quality conditions was noted and that these conditions addressed instances where usual data was missing due to the developing nature of the vaccine. The quality conditions align with those required by other regulators, in particular the European Medicines Agency.

Medsafe noted that under Emergency Use Authorisation procedures, product released to the US and UK markets are from smaller batch sizes.

The scale difference of the potential New Zealand batches was a focus of the quality data assessment to ensure vaccine manufactured at commercial scale is comparable to clinical trial batches.

Pfizer has demonstrated that final product specifications are sufficient to ensure that product supplied to New Zealand will be comparable to clinical trial batches. Any gaps in product characterisation would be covered in the conditions of the provisional consent.

The Committee expressed confidence in the Medsafe quality and manufacturing evaluation and were interested in being kept informed of updates in this area.

- **Clinical evaluation report**

The Committee considered the following documentation:

  - Final evaluation report – Clinical

The Committee considered the issue of efficacy data for subpopulations. This subset included Maori, Asian, Pacific peoples, the elderly and groups who are immunocompromised. The Committee commented that the ethnicity subset data submitted was remarkably similar in efficacy and it is not unreasonable to assume there is no genetic reason for different responses in different ethnic groups in New Zealand.

The Committee agreed that it will be important to collect post-market safety data for Maori, Pacific peoples, elderly and immunocompromised subsets as these are the people who are more likely to be at higher risk of complications of COVID-19. However, the clinical picture on efficacy and safety will become clearer over time as more people receive the vaccine.

The Committee discussed the lack of data on the duration of response of the vaccine. Medsafe had asked the sponsor for an early cut-off time for more data, which was not available. The sponsor had confirmed that the next data analysis from the pivotal clinical trial will arrive in April 2021.

Overall, the Committee was satisfied with the clinical report and summary presented. The Committee was satisfied with the efficacy data to date acknowledging that more data will be available over time.

- **RMP evaluation report**

The Committee considered the following documentation:

  - Final evaluation report - RMP

The Committee considered that the latest version of the Risk Management Plan addresses many areas of concern raised by Medsafe. The need for additional safety information regarding the elderly, children, people with comorbidities and immunocompromised people was emphasised.

The Committee noted that patients with autoimmune diseases and patients who are immunosuppressed were not well represented in clinical trials. The planned clinical study in patients with rheumatoid arthritis receiving

immunomodulators was noted. The Committee expressed concern that these individuals might be among those prioritised for vaccination before the results of this study are available. It was noted that this issue is to be managed as part of the Ministry of Health immunisation implementation programme.

The need for more information on potential safety signals such as reactogenicity, anaphylaxis, vaccine-associated enhanced disease and facial paralysis was noted.

The Committee was satisfied with the updated Risk Management Plan, noting that additional clinical studies, pharmacovigilance activities and monthly safety reports are planned to address areas of missing information.

The Committee accepted the Risk Management Plan as written, noting that it is a living document and there is the opportunity to add safety concerns as they emerge.

***Discussion with Pfizer***

Pfizer representatives joined the meeting to respond to questions from the Committee. The Committee had questions regarding finished product testing, risk of transport to New Zealand, in use data in specific populations, use in severe COVID-19, the emergence of new variants, unforeseen safety signals after the doses given to date, update on duration of protection and the new 6 dose proposal. All questions were suitably addressed by Pfizer.

***Discussion to finalise recommendation***

***Provisional Consent***

The Committee unanimously agreed to Medsafe's proposal to grant provisional consent with a nine-month period. This period was proposed to ensure that all post-approval data commitment deadlines were met. The Committee agreed with this rationale.

***Indications***

The Committee agreed that the proposed indication wording for Comirnaty is revised to the following:

> *Comirnaty has provisional consent (see section 5.1) 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 committee discussed the likely real world use in New Zealand and acknowledged that the vaccine roll-out will be managed by the Ministry of Health.

The Committee suggested that Section 5.1 of the data sheet to be revised to include the following statement:

> *This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.*

***Conditions of provisional consent***

The Committee reviewed each proposed condition of the provisional consent. The Committee agreed that Medsafe could make technical amendments to the conditions of consent.

The Committee agreed to the addition of the following condition:

> *Provide independent batch certification, such as UK National Institute for Biological Standards and Control (NIBSC) certification, EU Official Control Authority Batch Release (OCABR) certification, Australian TGA batch release assessment, or any other certification agreed with Medsafe, on request for all batches distributed in New Zealand.*

The Committee raised concerns regarding the wording of the following conditions.

> *Provide regular updates on the duration of efficacy and the requirement for booster doses. This should include the six months analysis data from Study C4591001. Interim report due: April 2021.*
>
> *Provide updates on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, when these become available.*
>
> *Submit the final Clinical Study Reports for Study C4591001 and Study BNT162-01 once they available.*
>
> *Inform Medsafe of all safety reviews they conduct or become aware of and provide the completed review.*

The Committee recommended the following amendments to the conditions to improve clarity of the requirements:

> *Provide regular reports on the duration of efficacy and the requirement for booster doses within five working days of these being produced.*

*Provide the six months analysis data from Study C4591001. Report due: April 2021.*

*Provide any reports on efficacy including regarding asymptomatic infection in the vaccinated group, vaccine failure, immunogenicity, efficacy in population subgroups and results from post-marketing studies, within five working days of these being produced.*

*Provide the final Clinical Study Reports for Study C4591001 and Study BNT162-01 within five working days of these being produced.*

*Provide monthly safety reports, as well as all safety reviews they conduct or become aware of.*

***Recommendation***

The Committee recommended that the Minister of Health should grant provisional consent to distribute this medicine under Section 23 of the Medicines Act 1981 and impose the conditions proposed by Medsafe as amended by the Committee. The Committee recommended that the provisional consent should have an effect of nine months.

***General Business***

The Chair thanks s 9(2)(g)(ii) for his services to the Committee and wishes him well in his future endeavours.

***Date of Next Meeting***
No date has been set.

There being no further business, the Chair thanked members and guests for their attendance and closed the meeting at 2.14pm.

**CHAIR'S SIGNATURE:** s 9(2)(g)(ii) [redacted]

**DATE:** 03/02/2021

This document was prepared and written by
s 9(2)(g)(ii) [redacted]
the Medicines Assessment Advisory Committee Secretary

# SUMMARY OF RECOMMENDATIONS FROM THE 109TH MEETING OF THE MEDICINES ASSESSMENT ADVISORY COMMITTEE HELD IN WELLINGTON ON TUESDAY 2 FEBRUARY 2021 AT 9:30 AM

## 4. Applications for consent to distribute a new medicine under section 23 of the Medicines Act 1981 (referred by the Minister of Health under section 22(2))

**4.1** The Committee recommended that the Minister of Health should grant provisional consent to distribute this medicine under Section 23 of the Medicines Act 1981 and impose the conditions proposed by Medsafe as amended by the Committee. The Committee recommended that the provisional consent should have an effect of nine months.

.

133 Molesworth Street
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T +64 4 496 2000
W www.medsafe.govt.nz

3 February 2021

s 9(2)(a)
Senior Regulatory Affairs Associate, Global Regulatory Affairs – International
Pfizer New Zealand Limited
P O Box 3998
AUCKLAND 1140

File Ref: TT50 10853

Dear s 9(2)(a)

**MAAC recommendation to grant provisional consent to distribute a new medicine under section 23 of the Medicines Act 1981 – Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech) 0.5 mg/mL concentrate for injection (TT50-10853)**

This letter is to notify you that your application for consent to distribute the above medicine was referred to the Medicines Assessment Advisory Committee (MAAC) and considered at its meeting held on 2 February 2021.

The Committee's recommendation is that I, as the Minister's delegate, should grant provisional consent to the distribution of the medicine. I agree with the MAAC's recommendation and a provisional consent notice will be submitted for publication in the *New Zealand Gazette.* Please confirm with the MAAC Secretary (at committees@health.govt.nz), that the details in the enclosed Therapeutic Product Database Report are correct.

Please note that the provisional consent to distribute a medicine does not take effect until the date of publication of the *Gazette* notice. Electronic copies of the final data sheet(s) and declaration form(s) must be submitted to Medsafe within 10 days of publication of the *Gazette* notice. You will be sent a letter advising you when publication has occurred, with a copy of the *Gazette* notice enclosed.

Yours sincerely

Chris James
Group Manager
Medsafe
as the Minister's delegate for section 20/23 of the Medicines Act 1981

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Yours sincerely

Chris James
Group Manager
Medsafe
as the Minister's delegate for section 20/23 of the Medicines Act 1981