

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

COMIRNATY® Original/Omicron BA.4-5 (tozinameran/famtozinameran), 0.1 mg/mL suspension for injection (15/15 micrograms/0.3 mL dose)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial. **Do not dilute prior to use.**

One vial (2.25 mL) contains 6 doses of 0.3 mL, see Section 4.2 Dose and method of administration and Section 6.6 Special precautions for disposal and other handling.

1 dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Tozinameran and famtozinameran are single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Original and Omicron BA.4-5).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Suspension for injection.

The vaccine is a white to off-white frozen suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMIRNATY Original/Omicron BA.4-5 vaccine has provisional consent (see section 5.1) for the indication below:

A booster dose for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

The use of this vaccine should be in accordance with official recommendations.

4.2 Dose and method of administration

Dose

The dose of Comirnaty Original/Omicron BA.4-5 is 0.3 mL given intramuscularly.

Booster dose in individuals 12 years of age and older

A booster dose of COMIRNATY Original/Omicron BA.4-5 may be administered intramuscularly at least 5 months after the primary course in individuals 12 years of age and older.

If required, any subsequent booster dose may be administered as early as 4 months after last administration of a booster dose.

The decision when and for whom to implement a booster dose of COMIRNATY Original/Omicron BA.4-5 should be made in accordance with official recommendations (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

Heterologous booster dose:

COMIRNATY Original/Omicron BA.4-5 may also be given as a booster dose in individuals 18 years of age and older who have received a primary course comprised of another COVID-19 vaccine.

Primary vaccination course

COMIRNATY Original/Omicron BA.4-5 is indicated only for booster doses.

For details on the primary vaccination course for ages 12 and above, please refer to the Data sheets for COMIRNATY 30 micrograms/dose for injection.

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

COMIRNATY Original/Omicron BA.4-5 should be administered intramuscularly. The preferred site of administration is the deltoid muscle of the upper arm.

Do not inject COMIRNATY Original/Omicron BA.4-5 intravascularly, subcutaneously or intradermally.

COMIRNATY Original/Omicron BA.4-5 should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering COMIRNATY Original/Omicron BA.4-5, see Section 4.4 Special warnings and precautions for use.

Vials have a grey cap, contain six doses of 0.3 mL of vaccine and **do not require dilution**. In order to extract six doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.

- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

For instructions on thawing, handling and dose preparation of COMIRNATY Original/Omicron BA.4-5, see Section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 the vaccine.

The individual should be kept under close observation for at least 15 minutes following vaccination. COMIRNATY Original/Omicron BA.4-5 should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often, but not exclusively in younger men. There have been reports in females. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. The cases are generally mild and individuals tend to recover within a short time following standard treatment and rest. Cases of myocarditis and pericarditis following vaccination have rarely been associated with severe outcomes including death.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis, including atypical presentations. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Non-specific symptoms of myocarditis and pericarditis also include fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Stress-related responses

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine 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.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of the vaccine may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with COMIRNATY Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of the vaccine.

Use in the elderly

The safety and effectiveness of a booster dose of COMIRNATY Original/Omicron BA.4-5 is based on safety and effectiveness data of COMIRNATY Original/Omicron BA.1.

Clinical studies of COMIRNATY Original/Omicron BA.1 include participants 55 years of age and older and their data contributes to the overall assessment of safety and efficacy. See Section 5.1 Pharmacodynamic properties, Clinical trials, Efficacy against COVID-19. No dosage adjustment is required in elderly individuals ≥ 65 years of age.

The data for use in the frail elderly (>85 years) is limited. The potential benefits of vaccination versus the potential risk and clinical impact of even relatively mild systemic adverse events in the frail elderly should be carefully assessed on a case-by-case basis.

Paediatric use

The safety and effectiveness of a booster dose of COMIRNATY Original/Omicron BA.4-5 is based on safety and effectiveness data of COMIRNATY Original/Omicron BA.1.

The safety and efficacy of COMIRNATY Original/Omicron BA.1 in children aged less than 12 years of age have not yet been established.

The safety and effectiveness of a booster dose of COMIRNATY Original/Omicron BA.1 in individuals 12 to 17 years of age is based on safety and effectiveness data in adults at least 18 years of age.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed.

Concomitant administration of COMIRNATY with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Fertility

In a combined fertility and developmental toxicity study, female rats were intramuscularly administered tozinameran prior to mating and during gestation (4 full human doses of 30 micrograms each, spanning between pre-mating day 21 and gestation day 20). SARS-CoV-2 neutralising antibodies were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in fetuses and offspring. There were no vaccine related effects on female fertility and pregnancy rate.

Pregnancy

No data are available yet regarding the use of COMIRNATY Original/Omicron BA.4-5 during pregnancy.

There is limited experience with use of tozinameran 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 4.6 Fertility, pregnancy and lactation, Fertility). Administration of the vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Lactation

No data are available yet regarding the use of COMIRNATY Original/Omicron BA.4-5 during breast-feeding.

It is unknown whether tozinameran or famtozinameran is excreted in human milk. A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see Section 4.6 Fertility, pregnancy and lactation, Fertility).

4.7 Effects on ability to drive and use machines

COMIRNATY Original/Omicron BA.4-5 has no, or negligible, influence on the ability to drive and use machines. However, some of the effects mentioned under Section 4.8 Undesirable effects may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran)

Participants 12 years of age and older – after bivalent Omicron BA.4-5 booster dose

In a subset from Study C4591044 (Cohort 2), 316 individuals 12 years of age and older who had completed 3 doses of COMIRNATY, received a booster (fourth dose) of COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms). In a subset of Study C4591044, 107 participants 12 to 17 years of age, 103 participants 18 to 55 years of age and 106 participants 56 years of age and older previously vaccinated with a 2-dose primary series and 1 booster dose of COMIRNATY (tozinameran) went on to receive a second booster dose with COMIRNATY Original/Omicron BA.4-5. The participants 12 years of age and older who received a second booster dose with the COMIRNATY Original/Omicron BA.4-5 received it 5.5 to 14.3 months after receiving the first booster dose and had a median follow up time of 1.6 months up to a data cut-off date of October 12, 2022.

The overall safety profile for the COMIRNATY Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after the COMIRNATY booster (third dose). Adverse reactions following administration of Comirnaty Original/Omicron BA.4-5 as a second booster dose included pain at the injection site (68.5%), fatigue (56.4%), headache (41.4%), muscle pain (25.8%), chills (16.9%), joint pain (13.4%), fever (7.3%), injection site swelling (5.4%), injection site redness (4.8%), and lymphadenopathy (0.3%).

COMIRNATY Original/Omicron BA.1 (tozinameran/riltozinameran)

Participants 55 years of age and older – after bivalent Omicron BA.1 booster dose

In a subset from Study C4591031 (Phase 3), 305 adults greater than 55 years of age who had completed 3 doses of COMIRNATY, received a booster (fourth dose) of COMIRNATY Original/Omicron BA.1 (15/15 micrograms) 4.7 to 11.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of COMIRNATY Original/Omicron BA.1 had a median follow-up time of at least 1.7 months.

The overall safety profile for the COMIRNATY Original/Omicron BA.1 booster (fourth dose) was similar to that seen after the COMIRNATY booster (third dose). The most frequent adverse reactions in participants greater than 55 years of age were injection site pain (> 50%), fatigue (> 40%), headache (> 30%), myalgia (> 20%), chills and arthralgia (> 10%). No new adverse reactions were identified for COMIRNATY Original/Omicron BA.1.

Participants 18 to ≤55 years of age – after monovalent Omicron BA.1 booster dose

The safety of a COMIRNATY Original/Omicron BA.1 booster dose in individuals from 18 to ≤ 55 years of age is extrapolated from safety data from a subset of 315 adults 18 to ≤ 55 years of age who received a booster (fourth dose) of Omicron BA.1 30 micrograms (monovalent) after completing 3 doses of COMIRNATY. The most frequent adverse reactions in these participants 18 to ≤55 years of age were injection site pain (> 70%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills (> 30%) and arthralgia (> 20%).

COMIRNATY (tozinameran)

The safety of COMIRNATY was evaluated in participants 5 years of age and older in 3 clinical studies that included 24,675 participants (comprised of 22,026 participants 16 years of age and older, 1,131 adolescents 12 to 15 years of age and 1,518 children 5 to 11 years of age) that have received at least one dose of COMIRNATY.

Additionally, 306 existing Phase 3 participants at 18 to 55 years of age received a booster dose of COMIRNATY approximately 6 months after the second dose in the non-placebo-controlled booster dose portion of Study C4591001. The overall safety profile for the booster dose was similar to that seen after 2 doses.

In Study C4591031, a placebo-controlled booster study, 5,081 participants 16 years of age and older were recruited from Study C4591001 to receive a booster dose of COMIRNATY at least 6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.

Participants 16 years of age and older – after 2 doses

In Study C4591001, a total of 22,026 participants 16 years of age or older received at least 1 dose of COMIRNATY 30 micrograms and a total of 22,021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the COMIRNATY and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of COMIRNATY.

At the time of the analysis of Study C4591001 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25,651 (58.2%) participants (13,031 COMIRNATY and 12,620 placebo) 16 years of age and older were followed up for ≥4 months after the second dose. This included a total of 15,111 (7,704 COMIRNATY and 7,407 placebo) participants 16 to 55 years of age and a total of 10,540 (5,327 COMIRNATY and 5,213 placebo) participants 56 years and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and 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 safety profile in 545 subjects receiving COMIRNATY, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Study C4591001 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving

COMIRNATY (n=100) in the individuals with stable HIV infection was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long term safety follow-up in Study C4591001, 2,260 adolescents (1,131 COMIRNATY 30 micrograms; 1,129 placebo) were 12 to 15 years of age. Of these, 1,559 adolescents (786 COMIRNATY and 773 placebo) have been followed for ≥ 4 months after the second dose of COMIRNATY. The safety evaluation in Study C4591001 is ongoing.

The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).

Participants 16 years of age and older – after booster dose

A subset from Study C4591001 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original COMIRNATY 2-dose course, received a booster dose of COMIRNATY approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

In Study C4591031, a placebo-controlled booster study, participants 16 years of age and older recruited from Study C4591001 received a booster dose of COMIRNATY (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of COMIRNATY. Overall, participants who received a booster dose, had a median follow-up time of 2.5 months after the booster dose to the cut-off date (5 October 2021).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common ($\geq 1/10$),

Common ($\geq 1/100$ to $< 1/10$),

Uncommon ($\geq 1/1,000$ to $< 1/100$),

Rare ($\geq 1/10,000$ to $< 1/1,000$),

Very rare ($< 1/10,000$),

Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from COMIRNATY and COMIRNATY Original/Omicron BA.1 clinical trials: Individuals 12 years of age and older

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy ^a		
Metabolism and nutrition disorders			Decreased appetite		
Psychiatric disorders			Insomnia		
Nervous system disorders	Headache		Lethargy	Acute peripheral facial paralysis ^b	
Gastrointestinal disorders		Nausea;			
Skin and subcutaneous tissue disorders			Hyperhidrosis; Night sweats		
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia				
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia ^c ; Injection site swelling	Injection site redness	Asthenia; Malaise;		Facial swelling ^d

^a A higher frequency of lymphadenopathy (2.8% vs 0.4%) was observed in participants receiving a booster dose in Study C4591031 compared to participants receiving 2 doses.

^b Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COMIRNATY group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

^c A higher frequency of pyrexia was observed after the second dose compared to the first dose. The preferred term pyrexia is a cluster term covering also body temperature increased.

^d Facial swelling in vaccine recipients with a history of injection of dermatological fillers

Post-marketing experience

Although the events listed in Table 2 were not observed in the clinical trials, they are considered adverse drug reactions for COMIRNATY as they were reported in the post-marketing experience. As these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

Table 2: Adverse reactions from COMIRNATY post marketing experience

System Organ Class	Adverse Drug Reaction
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g. rash, pruritis, urticaria, angioedema)
Cardiac disorders	Myocarditis Pericarditis
Nervous system disorder	Dizziness
Gastrointestinal disorders	Diarrhoea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm) ^a
General disorders and administration site conditions	Extensive swelling of vaccinated limb

^a A higher frequency of pain in extremity (1.1% vs. 0.8%) was observed in participants receiving a booster dose in Study C4591031 compared to participants receiving 2 doses.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of COMIRNATY. The COMIRNATY recipients did not report an increase in reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, other viral vaccines, ATC code: J07BX03.

Mechanism of action

The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 spike (S) antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralising antibody and cellular immune responses to the antigen, which may contribute to protection against COVID-19.

Clinical efficacy and safety

COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran)

Immunogenicity in participants 18 years of age and older – after bivalent Original/Omicron BA.4-5 (second booster dose)

In a descriptive analysis of a subset from Study C4591044 (Cohort 2), 95 participants 18 to 55 years of age and 102 participants 56 years of age and older who had previously received a 2-dose primary series and 1 booster dose with COMIRNATY received COMIRNATY Original/Omicron BA.4-5. COMIRNATY Original/Omicron BA.4-5 booster dose was administered 5.6 to 12.8 months (median 10.9 months) in participants 18 to 55 years of age and 5.5 to 13.0 months (median 11.0 months) in participants 56 years of age and older after the first booster dose. In participants 18 to 55 years of age and 56 years of age and older, 65.3% and 60.8% were positive for SARS-CoV-2 at baseline, respectively.

The study assessed the level of NT50 of the anti-Omicron BA.4/BA.5, anti-Omicron BA.1, and Original SARS COV-2 strains. A descriptive summary of GMTs is provided in Table 3. Immunogenicity results are based on validated assays for 50% SARS-CoV-2 neutralizing titers against Omicron BA.4/BA.5, Omicron BA.1 and the reference strain (USA-WA-1/2020) titers from before study vaccination (dose 4) to 1 month after study vaccination (dose 4) among adults 18 to 55 and >55 years of age who received a booster (dose 4) of COMIRNATY Original/Omicron BA.4-5 (15/15micrograms) in C4591044 Cohort 2.

Table 3: Geometric Mean Titers by Baseline SARS-CoV-2 Status – COMIRNATY Original/Omicron BA.4-5 Groups Subset of Study C4591044 – Comparison of Prior to the Second Booster Dose to 1 Month After Second Booster – Participants 18 Years of Age and Older – Evaluable Immunogenicity Population

Assay	Baseline SARS-CoV-2 Status	Sampling Time Point ^a	COMIRNATY Original/Omicron BA.4-5			
			18-55 years		>55 years	
			n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
SARS-CoV-2 neutralisation assay - Omicron BA.4/BA.5 - NT50 (titre) ^f	All	Prevac	95	338.3 (238.1, 480.7)	101	301.9 (215.6, 422.8)
		1 Month	95	2839.0 (2150.0, 3748.8)	102	3001.1 (2318.2, 3885.1)
	Positive ^d	Prevac	62	900.3 (661.5, 1225.2)	61	745.8 (516.5, 1076.9)
		1 Month	62	4678.4 (3438.9, 6364.6)	62	4383.6 (3261.9, 5891.1)
	Negative ^e	Prevac	33	53.8 (41.1, 70.5)	40	76.0 (54.7, 105.7)
		1 Month	33	1110.7 (743.9, 1658.4)	40	1668.1 (1089.6, 2553.7)
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre) ^f	All	Prevac	95	346.0 (240.0, 498.9)	102	365.1 (260.8, 511.1)
		1 Month	95	2407.2 (1884.9, 3074.2)	102	2656.1 (2089.6, 3376.3)
	Positive ^d	Prevac	62	934.3 (697.0, 1252.5)	62	937.3 (689.5, 1274.0)
		1 Month	62	3938.2 (3069.0, 5053.5)	62	3871.0 (2919.8, 5132.2)

Assay	Baseline SARS-CoV-2 Status	Sampling Time Point ^a	COMIRNATY Original/Omicron BA.4-5			
			18-55 years		>55 years	
			n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
SARS-CoV-2 neutralisation assay - reference strain - NT50 (titre) ^f	Negative ^e	Prevax	33	53.5 (35.0, 81.8)	40	84.7 (55.7, 128.6)
		1 Month	33	954.7 (664.4, 1371.8)	40	1481.5 (1020.3, 2151.2)
	All	Prevax	95	2349.0 (1693.4, 3258.4)	101	2643.1 (1990.8, 3509.1)
		1 Month	95	11919.3 (9839.1, 14439.3)	102	12103.8 (9992.0, 14662.0)
	Positive ^d	Prevax	62	5615.4 (4406.4, 7156.1)	61	5428.8 (4112.6, 7166.3)
		1 Month	62	16214.4 (13340.3, 19707.6)	62	15336.7 (12079.9, 19471.6)
Negative ^e	Prevax	33	456.8 (291.5, 716.0)	40	881.9 (601.6, 1292.7)	
	1 Month	33	6685.8 (4731.8, 9446.9)	40	8386.3 (6235.4, 11279.2)	

Abbreviations: GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
- Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.1 and BA.4/BA.5).

COMIRNATY Original/Omicron BA.1 (tozinameran/riltozinameran)

Relative vaccine immunogenicity in participants greater than 55 years of age – after bivalent Omicron BA.1 booster dose

In an interim analysis of a subset from Study C4591031 (Substudy E), 610 adults greater than 55 years of age who had completed a series of 3 doses of COMIRNATY received 1 of the following as a booster dose (fourth dose): COMIRNATY (30 micrograms) or COMIRNATY Original/Omicron BA.1 (15/15micrograms). GMRs and seroresponse rates were evaluated at 1 month after COMIRNATY Original/Omicron BA.1 (15/15 micrograms) booster vaccination up to a data cut-off date of 16 May 2022, which represents a median of at least 1.7 months post-booster follow-up. The COMIRNATY Original/Omicron BA.1 (15/15 micrograms) booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the third dose.

The primary objective of the analysis was to assess superiority with respect to level of neutralising titre and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of COMIRNATY Original/Omicron BA.1 (15/15 micrograms) relative to the response elicited by a dose of COMIRNATY (30 micrograms) given as a fourth dose in COMIRNATY-experienced participants greater than 55 years of age.

Superiority of COMIRNATY Original/Omicron BA.1 (15/15 micrograms) to COMIRNATY (30 micrograms) were met, as the lower bound of the 2-sided 95% CI for GMR was > 1 (but < 1.5).

Table 4: Substudy E - Geometric mean ratios for between vaccine group comparison – participants without evidence of infection up to 1 month after Dose 4 – expanded cohort – immunogenicity subset – participants greater than 55 years of age – evaluable immunogenicity population

Assay	Vaccine group (as randomised)	Sampling time point ^a	N ^b	GMT (95% CI) ^c	GMR (95% CI) ^d
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre)	COMIRNATY (30 micrograms)	1 month	163	455.8 (365.9, 567.6)	
	COMIRNATY Original/Omicron BA.1 (15/15 micrograms)	1 month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

- Protocol-specified timing for blood sample collection.
- n = number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (vaccine group in the corresponding row - COMIRNATY [30 micrograms]) and the corresponding CI (based on the Student t distribution).

Table 5: Substudy E - Number (%) of participants achieving seroresponse – participants without evidence of infection up to 1 month after Dose 4 – expanded cohort – immunogenicity subset – participants greater than 55 years of age – evaluable immunogenicity population

Assay	Vaccine group (as randomised)	Sampling time point ^a	N ^b	n ^c (%) (95% CI) ^d	Difference % ^e (95% CI) ^f
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre)	COMIRNATY (30 micrograms)	1 month	149	85 (57.0) (48.7, 65.1)	
	COMIRNATY Original/Omicron BA.1 (15/15 micrograms)	1 month	169	121 (71.6) (64.2, 78.3)	14.6 (4.0, 24.9)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

Note: Seroresponse is defined as achieving ≥ 4 -fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

- Protocol-specified timing for blood sample collection.
- N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse at 1 month after vaccination for the given assay.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (vaccine group in the corresponding row - COMIRNATY [30 micrograms]).
- 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Relative vaccine immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose of COMIRNATY or monovalent Omicron BA.1

In a subset from Study C4591001 (Phase 3) and Study C4591031 (Phase 3), 315 participants 18 to ≤ 55 years of age who had completed 3 doses of COMIRNATY received a booster (fourth dose) of monovalent Omicron BA.1 90 to 180 days after receiving Dose 3. The median follow-up time after Dose 4 was 1.4 months (range: 1.0 to 1.7 months), except for 1 participant with a follow-up duration of < 1 month.

In the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after Dose 4, the ratio of GMTs for the monovalent Omicron BA.1 group to the COMIRNATY group GMR was 1.75 (2-sided 95% CI: 1.39, 2.22).

The lower bound of the 2-sided 95% CI for GMR was > 1, which meets the prespecified simple superiority criterion. Therefore, simple superiority of monovalent Omicron BA.1 to COMIRNATY for the Omicron variant was achieved based on the GMR at 1 month after Dose 4.

In participants without prior evidence of infection up to 1 month after Dose 4, the post hoc analysis of the difference in proportions of participants who achieved seroresponse between the monovalent Omicron BA.1 group and COMIRNATY group was 21.4% (2-sided 95% CI: 12.0, 30.4) (Table 7), similar to the results in the primary immunogenicity subset in which the noninferiority criterion (lower bound of the 2-sided 95% CI > -5) was achieved.

Table 6: Substudy D – Geometric mean ratios for between vaccine group comparison - cohort 2 - primary immunogenicity subset - participants without evidence of infection up to 1 month after Dose 4 - evaluable immunogenicity population

		Vaccine group (as randomised)			
		Monovalent Omicron BA.1 (30 micrograms)		COMIRNATY (30 micrograms)	
Assay	Dose/sampling time point ^a	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre)	1/1 month	132	1929.2 (1631.5, 2281.1)	141	1099.6 (932.0, 1297.4)

Abbreviations: GMT = geometric mean titre; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-first study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at the first study vaccination and the 1-month post-first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and

any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (monovalent Omicron BA.1 [30 micrograms] - COMIRNATY [30 micrograms]) and the corresponding CI (based on the Student t distribution).

Table 7: Substudy D – Difference in percentages of participants with seroresponse - cohort 2 - full expanded set - participants without evidence of infection up to 1 month after Dose 4 - evaluable immunogenicity population

		Vaccine group (as randomised)				Difference
		Monovalent Omicron BA.1 (30 micrograms)		COMIRNATY (30 micrograms)		
Assay	Dose/sampling time point ^a	N ^a	n ^b (%) (95% CI ^c)	N ^a	n ^b (%) (95% CI ^c)	% ^d (95% CI ^e)
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre)	1/1 month	206	127 (61.7) (54.6, 68.3)	226	91 (40.3) (33.8, 47.0)	21.4 (12.0, 30.4)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥ 4 -fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times$ LLOQ is considered seroresponse.

Note: Full expanded set = Cohort 2 excluding the sentinel group.

Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

- N = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculations.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (monovalent Omicron BA.1 [30 micrograms] - COMIRNATY [30 micrograms]).
- 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

COMIRNATY (tozinameran)

Study C4591001 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with HIV, hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study C4591001, based on data accrued through 14 November 2020, approximately 44,000 participants were randomised equally and were to receive 2 doses of COMIRNATY or placebo. The efficacy analyses included participants that

received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COMIRNATY. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins through to conclusion of the study in order to receive either placebo or COMIRNATY.

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the COMIRNATY group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COMIRNATY group and 68 in the placebo group) and 1616 participants 75 years of age and older (804 in the COMIRNATY group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2,214 person-years for the COMIRNATY group and in total 2,222 person-years for the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

COMIRNATY efficacy information is presented in Table 8.

Table 8: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COMIRNATY N ^a = 18,198 Cases n1 ^b Surveillance time ^c (n2 ^d)	Placebo N ^a = 18,325 Cases n1 ^b Surveillance time ^c (n2 ^d)	Vaccine efficacy % (95% CI) ^f
All participants ^e	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough,

new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- a. N = number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. No confirmed cases were identified in adolescents 12 to 15 years of age.
- f. Two-sided confidence interval (CI) for vaccine efficacy (VE) is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

In the second primary analysis, efficacy of COMIRNATY in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% credible interval of 89.9% to 97.3%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through 13 March 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.

The updated vaccine efficacy information is presented in Table 9.

Table 9: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COMIRNATY N^a=20,998 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=21,096 Cases n1^b Surveillance Time^c (n2^d)	Vaccine efficacy % (95% CI^e)
All participants ^f	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
16 to 64 years	70 4.859 (15,519)	710 4.654 (15,515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 to 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or

increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COMIRNATY group (both without and with or without evidence of prior SARS-CoV-2 infection); 16 and 18 in the placebo group (without and with or without evidence of prior SARS-CoV-2 infection, respectively).

Efficacy against severe COVID-19 in participants 12 years of age or older – after 2 doses

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 10) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COMIRNATY and placebo groups.

Table 10. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on Food and Drug Administration (FDA)[†] Definition After Dose 1 or From 7 Days After Dose 2 in the Placebo-Controlled Follow-up

	COMIRNATY Cases n1 ^a Surveillance Time (n2 ^b)	Placebo Cases n1 ^a Surveillance Time (n2 ^b)	Vaccine Efficacy % (95% CI ^c)
After Dose 1 ^d	1 8,439 ^c (22,505)	30 8,288 ^c (22,435)	96.7 (80.3, 99.9)
7 days after Dose 2 ^f	1 6,522 ^g (21,649)	21 6,404 ^g (21,730)	95.3 (70.9, 99.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

[†] Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;

- Death.
- a. n1 = Number of participants meeting the endpoint definition.
 - b. n2 = Number of participants at risk for the endpoint.
 - c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
 - d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
 - e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
 - f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician
 - g. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

An analysis of Study C4591001 has been performed in adolescents 12 to 15 years of age up to a data cutoff date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 11.

Table 11: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2 – participants without evidence of infection and with or without evidence of infection prior to 7 days after Dose 2 – adolescents 12 to 15 years of age evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY N^a = 1005 Cases n1^b Surveillance time^c (n2^d)	Placebo N^a = 978 Cases n1^b Surveillance time^c (n2^d)	Vaccine efficacy % (95% CI^e)
Adolescents 12 to 15 years	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age with or without* evidence of prior SARS-CoV-2 infection			
	COMIRNATY N^a = 1119 Cases n1^b Surveillance time^c (n2^d)	Placebo N^a = 1110 Cases n1^b Surveillance time^c (n2^d)	Vaccine efficacy % (95% CI^e)
Adolescents 12 to 15 years	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting).

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.

- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of subjects at risk for the endpoint.
- e. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time. CI not adjusted for multiplicity.

In Study C4591001 an analysis of SARS-CoV-2 neutralising titres in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to COMIRNATY in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 to 25 years of age (n = 170), based on results for SARS-CoV-2 neutralising titres at 1 month after Dose 2. The geometric mean titres (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67), which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.

An updated efficacy analysis of Study C4591001 has been performed in approximately 2,260 adolescents 12 to 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cut-off date of 2 September 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.

The updated vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 12.

Table 12: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 To 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY N^a=1057 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=1030 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI^e)
Adolescents 12 to 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	COMIRNATY N^a=1119 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=1109 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI^e)

Adolescents 12 to 15 years of age	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 100.0)
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Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity in participants 18 years of age and older – after booster dose

Effectiveness of a booster dose of COMIRNATY was based on an assessment of 50% neutralising titres (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study C4591001, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 to 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4 -fold rise in NT50 from baseline (before Dose 1). These analyses are summarised in Table 13.

Table 13. SARS-CoV-2 neutralisation assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 to 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[±]

	n	1 month after booster dose (95% CI)	1 month after primary series (95% CI)	1 month after booster dose/- 1 month after primary series (97.5% CI)	Met noninferiority objective (Y/N)
Geometric mean 50% neutralising titre (GMT)^b	212 ^a	2466.0 ^b (2202.6, 2760.8)	750.6 ^b (656.2, 858.6)	3.29 ^c (2.77, 3.90)	Y ^d
Seroresponse rate (%) for 50% neutralising titre[†]	200 ^e	199 ^f 99.5% (97.2%, 100.0%)	196 ^f 98.0% (95.0%, 99.5%)	1.5% ^g (-0.7%, 3.7% ^h)	Y ⁱ

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

[†] SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

- * Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Comirnaty) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.
- ± All eligible participants who had received 2 doses of Comirnaty as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
- a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
- b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
- d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
- e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
- f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
- g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
- h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
- i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose

An interim efficacy analysis of Study C4591031, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study C4591001, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. Vaccine efficacy of the COMIRNATY booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed. The relative vaccine efficacy information for participants 16 years of age and older is presented in Table 14.

Table 14: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination – Participants 16 Years of Age and Older With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection			
	COMIRNATY N^a=4993 Cases n¹^b Surveillance Time^c (n²^d)	Placebo N^a=4952 Cases n¹^b Surveillance Time^c (n²^d)	Relative Vaccine Efficacy^e % (95% CI^f)
First COVID-19 occurrence from 7 days after booster vaccination	7 0.871 (4934)	124 0.835 (4863)	94.6 (88.5, 97.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or

increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
- f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

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.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

Distearoylphosphatidylcholine (DSPC)

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6 Special precautions for disposal and other handling.

6.3 Shelf life

Unopened vial

Frozen vial

12 months when stored at -90°C to -60°C.

The vaccine will be received frozen at -90°C to -60°C. Frozen vaccine can be stored either at -90°C to -60°C or 2°C to 8°C upon receipt.

When stored frozen at -90°C to -60°C, 10-vial packs of the vaccine can be thawed at 2°C to 8°C for 6 hours or individual vials can be thawed at room temperature (up to 30°C) for 30 minutes.

Thawed vial

If the vaccine is received at 2°C to 8°C it should be stored at 2°C to 8°C. Once removed from frozen storage, the unopened vial may be stored refrigerated at 2°C to 8°C for a single period of up to 10 weeks within the 12-month shelf life.

Upon moving the product to 2°C to 8°C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

When stored frozen at -90°C to -60°C, the vaccine can be thawed at either 2°C to 8°C or at temperatures up to 30°C.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8°C to 30°C.

Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

Opened vial

Chemical and physical in-use stability has been demonstrated for 12 hours at 2°C to 30°C. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

COMIRNATY Original/Omicron BA.4-5 can be stored in a refrigerator at 2°C to 8°C for a single period of up to 10 weeks, not exceeding the original expiry date (EXP). The expiry date for storage at -90°C to -60°C is printed on the vial and outer carton after “EXP”.

Check that the expiry date has been updated to reflect the refrigerated EXP date and that the original expiry date has been crossed out.

Store in the original package to protect from light. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For detailed instructions see Section 6.6 Special precautions for disposal and other handling.

Once thawed, the vaccine cannot be re-frozen. Thawed vials can be handled in room light conditions.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3 Shelf life.

For additional advice on storing COMIRNATY Original/Omicron BA.4-5, contact Pfizer New Zealand on 0800 736 363.

6.5 Nature and contents of container

COMIRNATY Original/Omicron BA.4-5 2.25 mL fill volume, 2 mL clear multidose vial (Type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see Section 6.6 Special precautions for disposal and other handling.

Pack size: 10 vials, 195 vials

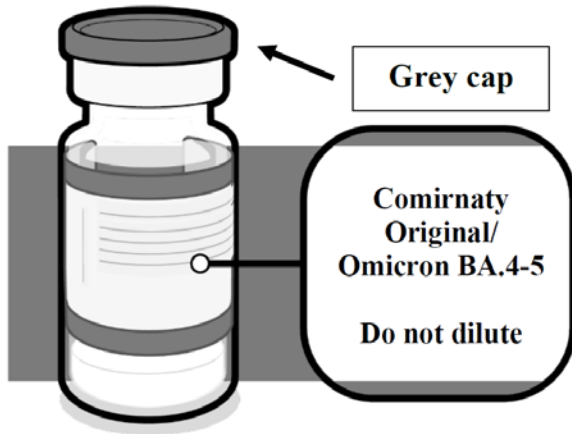
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared suspension.

COMIRNATY Original/Omicron BA.4-5 (grey cap, do not dilute)
Dose Verification

COMIRNATY Original/Omicron BA.4-5 (grey cap, do not dilute)



✓ Grey cap and label with grey border.

- Verify that the vial has a grey cap and a grey border around the label and the product name is COMIRNATY Original/Omicron BA.4-5 15/15 micrograms per dose suspension for injection.
- If the vial has a grey plastic cap and a grey border and the product name is COMIRNATY 30 micrograms/dose suspension for injection, please refer to the handling instructions in the Data sheet for COMIRNATY (Do Not Dilute).
- If the plastic cap and border around the label have another color, such as purple, orange, or maroon, please refer to the handling instructions in the Data sheet of these COMIRNATY vaccines.

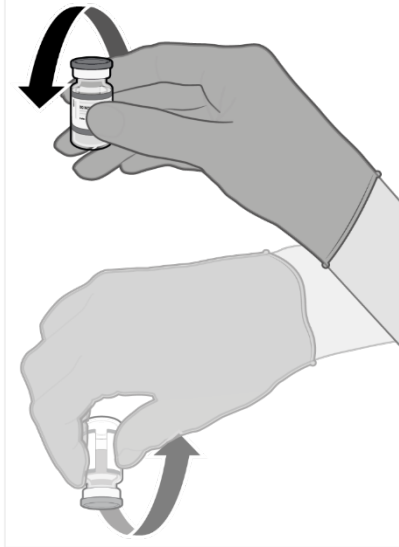
Handling Prior To Use



Store in the refrigerator for up to 10 weeks prior to use.

- If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 6 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

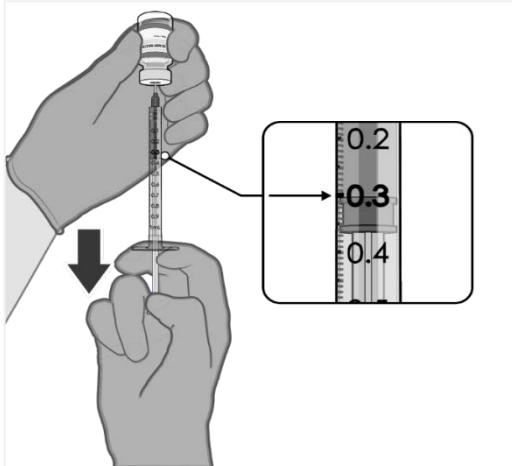
COMIRNATY Original/Omicron BA.4-5 (grey cap, do not dilute)



Gently × 10

- Gently mix by inverting vial 10 times prior to use. Do not shake.
- Prior to mixing, the thawed suspension may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white suspension with no particulates visible. Do not use the vaccine if particulates or discoloration are present.

Preparation of Individual 0.3 mL Doses



0.3 mL vaccine

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of COMIRNATY Original/Omicron BA.4-5.

Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters.

If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363
www.pfizermedinfo.co.nz

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute this medicine:

21 December 2022

10. DATE OF REVISION OF THE TEXT

N/A

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Summary of Updates

Section	Update
N/A	New Data sheet