SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

COMIRNATY 30 micrograms/dose concentrate for dispersion for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a purple cap and must be diluted before use.

One vial (0,45 mL) contains 6 doses of 0,3 mL after dilution, see sections 4.2 and 6.6.

One dose (0,3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA vaccine (embedded in lipid nanoparticles).

Tozinameran is a 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 SARS-CoV-2.

Contains sugar (sucrose).

Excipients with known effect

Each 0,3 mL dose contains 6 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).

The vaccine is a white to off-white frozen dispersion (pH: 6,9 – 7,9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMIRNATY 30 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

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

4.2 Posology and method of administration

Posology

Primary vaccination course

Individuals 12 years of age and older

COMIRNATY is administered intramuscularly after dilution as a primary course of 2 doses (0,3 mL each). It is recommended to administer the second dose 3 weeks after the first dose (see sections 4.4 and 5.1).

Severely immunocompromised aged 12 years and older

A third primary course dose may be administered intramuscularly at least 28 days after the second dose to individuals who are severely immunocompromised (see section 4.4).

Interchangeability

The interchangeability of COMIRNATY with COVID-19 vaccines from other manufacturers to complete the primary course has not been established. Individuals who have received ~~1~~a dose of COMIRNATY should continue to receive COMIRNATY to complete the primary course.

Doses of COMIRNATY 30 micrograms/dose concentrate for dispersion for injection after dilution (supplied in a vial with a purple cap) and COMIRNATY READY TO USE ADULT VACCINE 30 micrograms/dose dispersion for injection (supplied in a vial with a grey cap) are considered interchangeable.

Booster dose

The booster dose of COMIRNATY is 0,3 mL given intramuscularly.

A booster dose may be given in individuals 12 years of age and older. There should be an interval of at least 3 months between administration of COMIRNATY and the last prior dose of a COVID-19 vaccine.

Special populations

Elderly

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

Paediatric population

There is a paediatric formulation available for individuals 5 to 11 years of age (i.e. 5 to less than 12 years of age). For details, please refer to the professional information for COMIRNATY DILUTE TO USE PAEDIATRIC VACCINE 10 micrograms/dose concentrate for dispersion for injection.

The safety and efficacy of COMIRNATY in infants aged less than 6 months have not yet been established.

Method of administration

COMIRNATY 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of COMIRNATY contain six doses of 0,3 mL of vaccine. 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

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicines.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to COVID-19 mRNA vaccine (nucleoside modified) or to any of the excipients listed in section 6.1 [((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315); 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159); 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); cholesterol; potassium chloride; potassium dihydrogen phosphate sodium chloride; disodium phosphate dihydrate; sucrose; water for injections; sodium hydroxide and hydrochloric acid].

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicines, the name and the batch number of the administered medicine 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.

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of COMIRNATY.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with COMIRNATY. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general (see section 4.8).

Medical practitioners should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) 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.

Medical practitioners should consult guidance and/or specialists to diagnose and treat this condition.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are 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

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

The recommendation to consider a third dose in severely immunocompromised individuals is based on limited serological evidence from a case series in the literature from the clinical management of patients with iatrogenic immunocompromisation after solid organ transplantation (see section 4.2).

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

Vaccination with COMIRNATY may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

Excipients

COMIRNATY contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

COMIRNATY contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Refer to sections 4.3 or 6.1 for the full list of excipients.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with COMIRNATY during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). COMIRNATY can be used during pregnancy.

Breastfeeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of breastfeeding woman to COMIRNATY is negligible. Observational data from women who were breastfeeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. COMIRNATY can be used during breastfeeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

COMIRNATY has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Participants 16 years of age and older - after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of COMIRNATY 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 vaccine 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 2 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 participants 16 years of age and older receiving COMIRNATY, that were seropositive for SARS-CoV-2 at baseline, 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 2, 2 260 adolescents (1 131 COMIRNATY and 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 2 is ongoing.

The overall safety profile of COMIRNATY in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. 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 12 years of age and older – after booster dose

The safety of a booster dose of COMIRNATY in participants 12 years of age and older is inferred from safety data from studies of a booster dose of COMIRNATY in participants 16 years of age and older.

A subset from Study 2 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. Overall, participants who received a booster dose, had a median follow-up time of 8,3 months (range 1,1 to 8,5 months) and 301 participants had been followed for ≥ 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. 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 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 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~~8 months (range 0,3 to 7,5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1 281 participants (895 COMIRNATY and 386 placebo) have been followed for ≥ 4 months after the booster dose of COMIRNATY. No new adverse reactions of COMIRNATY were identified.

Participants 12 years of age and older – after subsequent booster doses

The safety of a booster dose of COMIRNATY in participants 12 years of age and older is inferred from safety data from studies of a booster dose of COMIRNATY in participants 18 years of age and older.

A subset of 325 adults 18 to ≤ 55 years of age who had completed 3 doses of COMIRNATY, received a booster (fourth dose) of COMIRNATY 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of COMIRNATY had a median follow-up time of 1,4 months up to a data cut-off date of 11 March 2022.

The most frequent adverse reactions in these participants were injection site pain (> 70 %), fatigue (> 60 %), headache (> 40 %), myalgia and chills (> 20 %), and arthralgia (> 10 %).

In a subset from Study 4 (Phase 3), 305 adults > 55 years of age who had completed 3 doses of COMIRNATY, received a booster (fourth dose) of COMIRNATY 5 to 12 months after receiving Dose 3. Participants who received a booster (fourth dose) of COMIRNATY had a median follow-up time of at least 1,7 months up to a data cut-off date of 16 May 2022. The overall safety profile for the COMIRNATY booster (fourth dose) was similar to that seen after the COMIRNATY booster (third dose). The most frequent adverse reactions in participants > 55 years of age were injection site pain (> 60 %), fatigue (> 40 %), headache (> 20 %), myalgia and chills (> 10 %).

Booster dose following primary vaccination with another authorised COVID-19 vaccine

In 5 independent studies on the use of a COMIRNATY booster dose in individuals who had completed primary vaccination with another authorized COVID-19 vaccine (heterologous booster dose), no new safety issues were identified (see section 5.1).

Tabulated list of adverse reactions from clinical studies and post-authorisation in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: 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), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 1: Adverse reactions from COMIRNATY clinical trials in individuals 12 years of age and older

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy[a]

Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash, pruritus, urticaria[b], angioedema[b])
	Not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Very common	Headache
	Uncommon	Lethargy
	Rare	Acute peripheral facial paralysis[c]
Gastrointestinal disorders	Common	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis, night sweats
Musculoskeletal and connective tissue disorders	Very common	Arthralgia, myalgia
	Uncommon	Pain in extremity[d]
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding[f]

Post-marketing side effects

Nervous system disorders:	Paraesthesia, hypoaesthesia, dizziness
Cardiac disorders:	Myocarditis, pericarditis
Gastrointestinal disorders:	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders:	Erythema multiforme
General disorders and administration site conditions:	Extensive swelling of vaccinated limb, facial swelling[f]

f. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with COMIRNATY is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of COMIRNATY. One study showed that in a period of 7 days after the second dose there were about 0,265 (95 % CI 0,255 – 0,275) extra cases of myocarditis in 12 – 29-year-old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0,56 (95 % CI 0,37 – 0,74) extra cases of myocarditis in 16 – 24-year-old males per 10 000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with COMIRNATY in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

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 vaccine 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.

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 COVID-19 mRNA 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 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 spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 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 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA vaccine 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 COVID-19 mRNA vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma medicines or immunoglobulins through conclusion of the study in order to receive either placebo or COVID-19 mRNA vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA vaccine 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 COVID-19 mRNA vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA vaccine 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 COVID-19 mRNA vaccine and in total 2 222 person-years in 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/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2: 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	**COVID-19 mRNA Vaccine** **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)[fe]**
All participants	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 (3 848)	19 0,511 (3 880)	94,7 (66,7; 99,9)
65 to 74 years	1 0,406 (3 074)	14 0,406 (3 095)	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 1 000 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. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94,6 % (95 % confidence interval of 89,6 % to 97,6 %) 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 representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 3.

Table 3: 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

Subgroup	COVID-19 mRNA Vaccine 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 (4 192)	124 1,202 (4 226)	94,5 (88,3; 97,8)
65 to 74 years	6 0,994 (3 350)	98 0,966 (3 379)	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 1 000 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 95 % 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 COVID 19 mRNA Vaccine group; 16 in the placebo group

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91,1 % (95 % CI of 88,8 % to 93,0 %) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

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 4) 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 COVID-19 mRNA Vaccine and placebo groups.

Table 4: Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* or after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine 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[e] (22 505)	30 8,288[e] (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).

* 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 ≤ 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, non-invasive 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 1 000 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 1 000 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

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100 % (95 % confidence interval 75,3; 100,0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100 % (95 % confidence interval 78,1; 100,0).

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

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100 % (95 % confidence interval 86,8; 100,0) during the

period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100 % (95 % confidence interval 87,5; 100,0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n=190) to participants 16 to 25 years of age (n=170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1,76, with a 2-sided 95 % CI of 1,47 to 2,10. Therefore, the 1,5-fold non-inferiority criterion was met as the lower bound of the 2-sided 95 % CI for the geometric mean ratio [GMR] was > 0,67.

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

Effectiveness of a booster dose of COVID-19 mRNA vaccine was based on an assessment of 50 % neutralising antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 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 geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4-fold rise in NT50 from baseline (before primary series). These analyses are summarised in Table 5.

Table 5: SARS-CoV-2 neutralisation assay - NT50 (titer)† (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 through 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 non-inferiority objective (Y/N)
Geometric mean 50 % neutralizing titer (GMT[b])	212[a]	2 466,0[b] (2 202,6; 2 760,8)	755,7[b] (663,1; 861,2)	3,26[c] (2,76; 3,86)	Y[d]
Seroresponse rate (%) for 50 % neutralizing titer[†]	200[e]	199[f] 99,5 % (97,2 %; 100,0 %)	190[f] 95,0 % (91,0 %; 97,6 %)	4,5%[g] (1,0 %; 7,9 %[h])	Y[i]

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50 % neutralizing titer; 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 Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50 % of the virus is neutralized.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of COVID-19 mRNA Vaccine) 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 COVID-19 mRNA Vaccine as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of COVID-19 mRNA Vaccine, 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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0,5 × 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. Non-inferiority 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. Non-inferiority 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 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, 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. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the COVID-19 mRNA vaccine 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 without prior evidence of SARS-CoV-2 infection is presented in Table 6. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94,6 % (95 % confidence interval of 88,5 % to 97,9 %), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the COVID-19 mRNA vaccine group, and 124 primary cases in the placebo group.

Table 6: Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	COVID-19 mRNA vaccine **N[a]=4 695** **Cases** **n1[b]** **Surveillance Time[c] (n2[d])**	**Placebo** **N[a]=4 671** **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	6 0,823 (4 659)	123 0,792 (4 614)	95,3 (89,5; 98,3)

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 serological or virological evidence (prior to 7 days after receipt of the booster vaccination) 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 Visit 1 and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) 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 1 000 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 COVID-19 mRNA vaccine 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.

Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine

Effectiveness of a COMIRNATY booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N=51, mean age 54 ± 17), Janssen single dose (N=53, mean age 48 ±1 4), or COMIRNATY 30 mcg 2-dose series (N=50, mean age 50 ± 18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of COMIRNATY (30 mcg). The boost with COMIRNATY induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and COMIRNATY primary doses, respectively.

Heterologous boosting with COMIRNATY was also evaluated in the CoV-BOOST study (EudraCT 2021 002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age, interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21,6 fold with heterologous COMIRNATY booster (n=95).

Immunogenicity in participants > 55 years of age – after a booster dose (fourth dose) of COVID-19 mRNA Vaccine (30 mcg)

In an interim analysis of a subset from Study 4 (Substudy E), 305 participants > 55 years of age who had completed a series of 3 doses of COVID-19 mRNA Vaccine received COVID-19 mRNA Vaccine (30 mcg) as a booster dose (fourth dose) 5 to 12 months after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose (fourth dose) of COVID-19 mRNA Vaccine (30 mcg)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of COVID-19 mRNA Vaccine received COVID-19 mRNA Vaccine (30 mcg)

as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Table 7. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received COVID-19 mRNA Vaccine 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

	Dose/ sampling time point[a]	**Substudy D (18 to < 55 years of age)**		**Substudy E (> 55 years of age)**	
		COVID-19 mRNA Vaccine 30 mcg		**COVID-19 mRNA Vaccine 30 mcg**	
GMT		**N[b]**	**GMT (95 % CI[d])**	**N[b]**	**GMT (95 % CI[d])**
SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre)	1/Prevax	226	315,0 (269,0; 368,9)	167	67,5 (52,9; 86,3)
	1/1 Month	228	1063,2 (935,8; 1207,9)	163	455,8 (365,9; 567,6)
SARS-CoV-2 neutralization assay – reference strain – NT50 (titre)	1/Prevax	226	3999,0 (3529,5; 4531,0)	179	1389,1 (1142,1; 1689,5)
	1/1 Month	227	12009,9 (10744,3; 13424,6)	182	5998,1 (5223,6; 6887,4)
Seroresponse rate at 1 month post-Dose 4		**N[c]**	**n[e] (%) (95 % CI[f])**	**N[c]**	**n[e] (%) (95 % CI[f])**
SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre)	1/1 Month	226	91 (40,3 %) (33,8; 47,0)	149	85 (57,0 %) (48,7; 65,1)

SARS-CoV-2 neutralization assay – reference strain – NT50 (titre)	1/1 Month	225	76 (33,8 %) (27,6; 40,4)	179	88 (49,2 %) (41,6; 56,7)

Abbreviations: CI = confidence interval; 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: Median time from Dose 3 to Dose 4 of Comirnaty 30 mcg is 4,0 months for Substudy D Cohort 2 and 6,3 months for Substudy E expanded cohort.

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E 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.

Note: Seroresponse is defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the

LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered a seroresponse.

a. Protocol-specified timing for blood sample collection.
b. N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. 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.
d. 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 × LLOQ.
e. n = Number of participants with seroresponse for the given assay at the given sampling time point.
f. Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

See section 4.2.

5.2 Pharmacokinetic properties

Biodistribution results from a luciferase encoding modRNA formulated in the same LNP as BNT162b2, representative of the biodistribution of the modRNA LNP vaccine platform

After administration of an LNP-formulated luciferase-encoding modRNA to BALB/c mice by intramuscular (IM) injection of 1 µg each in the right and left hind leg (for a total of 2 µg), *in vivo* bioluminescence after injection of luciferin substrate was performed. Luciferase protein expression was detected at different timepoints at the site of injection and to a lesser extent, and more transiently (only seen at 6 hr post-injection), in the liver. Distribution to the liver is likely mediated by LNPs entering the blood stream. The luciferase expression at the injection sites dropped to background levels after 9 days.

The distribution of a LNP with a comparable lipid composition to BNT162b2 but with a surrogate luciferase RNA (monitoring the 3H-CHE lipid label), was investigated in blood, plasma and selected tissues in male and female Wistar Han rats over 48 hours after a single IM injection at 50 µg mRNA/animal. The greatest mean concentration of LNP was found remaining in the injection site at each time point in both sexes. Outside the injection site, low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1 - 4 hours post-dose. Over 48 hours, the LNP distributed mainly to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8 - 48 hours post-dose.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered COVID-19 mRNA vaccine (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with

an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/carcinogenicity

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

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered COVID-19 mRNA vaccine prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rats due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There was no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No COVID-19 mRNA vaccine data are available on vaccine placental transfer or excretion in milk.

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)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Potassium chloride

Potassium dihydrogen phosphate

Sodium chloride

Disodium phosphate dihydrate

Sucrose

Water for injections

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:

Frozen vial:

24 months at -90 °C to -60 °C.

Within the 24-month shelf life, unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C.

When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial:

1 month at 2 °C to 8 °C within the 24-month shelf life.

Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.

Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions once removed from the freezer

Stability data indicate that the unopened vial is stable for up to:

- 24 hours when stored at temperatures from -3 °C to 2 °C
- a total of 4 hours when stored at temperatures from 8 °C to 30 °C; this includes the 2 hours at up to 30 °C detailed above

This information is intended to guide health care providers only in case of temporary temperature excursion.

Transfers of frozen vials stored at ultra-low temperature (< -60 °C)

- *Closed-lid vial trays* containing 195 vials removed from ultra-low temperature frozen storage (< -60 °C) may

be at temperatures up to 25 °C for up to 5 minutes.

- *Open-lid vial trays,* or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C

- *Closed-lid vial trays* containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- *Open-lid vial trays*, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicine

Chemical and physical in-use stability, including during transportation, has been demonstrated for 6 hours at 2 ºC to 30 ºC after dilution in sodium chloride 9 mg/mL (0,9 %) solution for injection. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the medicine should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For storage conditions after thawing and dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

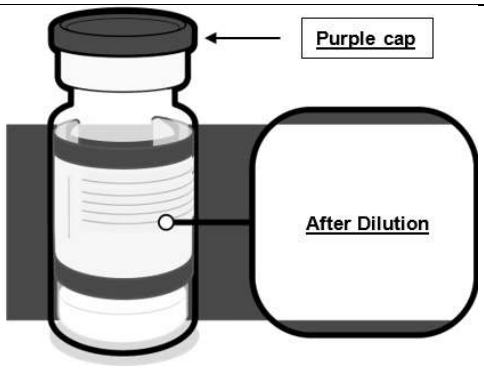
0,45 mL concentrate in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Each vial contains 6 doses (see section 6.6).

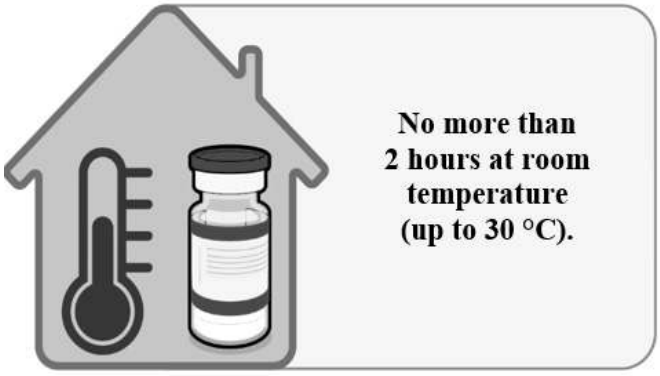
Pack size: 195 vials

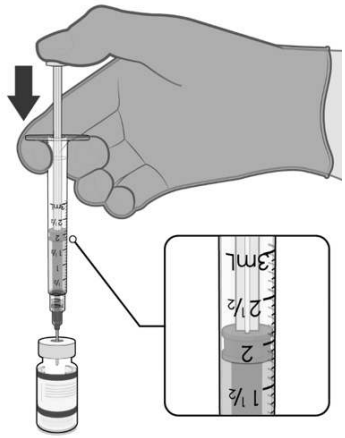
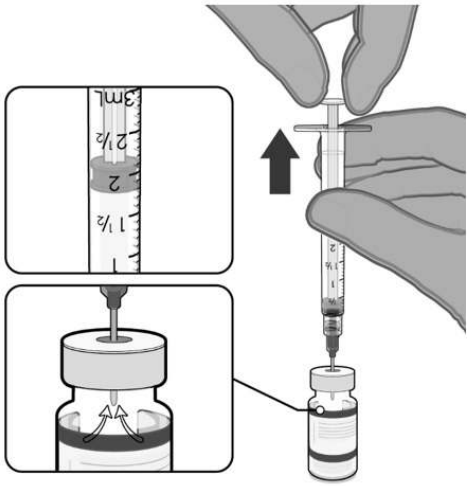
6.6 Special precautions for disposal and other handling

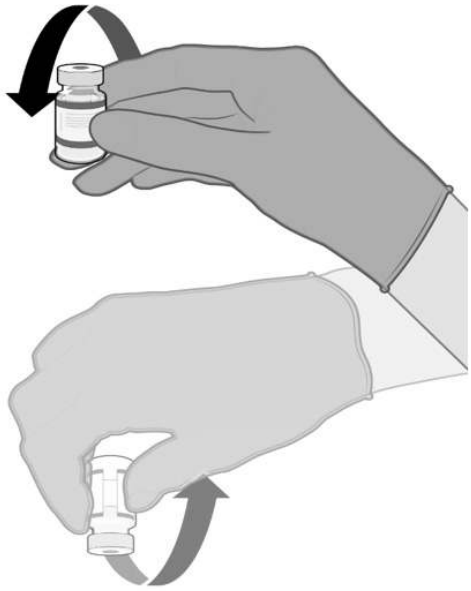
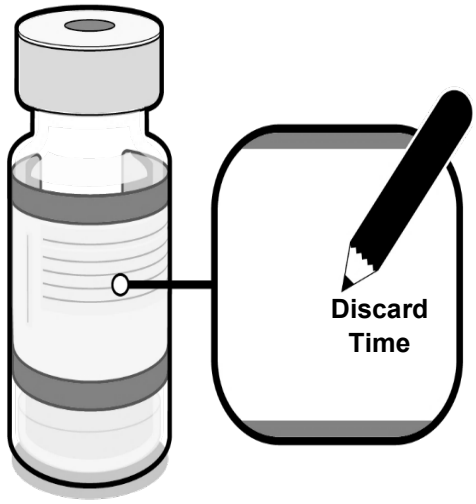
Handling instructions

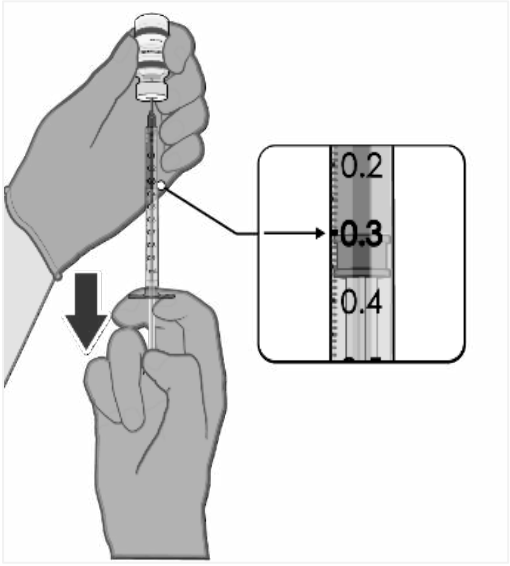
COMIRNATY should be prepared by a health care provider using aseptic technique to ensure the sterility of the prepared dispersion.

VIAL VERIFICATION OF COMIRNATY 30 MICROGRAMS/DOSE CONCENTRATE FOR DISPERSION FOR INJECTION (12 YEARS AND OLDER)	
	• Verify that the vial has a purple plastic cap. • If the vial has a grey plastic cap, please make reference to the professional information for COMIRNATY READY TO USE ADULT VACCINE 30 micrograms/dose dispersion for injection. • If the vial has an orange plastic cap, please make reference to the professional information for COMIRNATY-DILUTE TO USE PAEDIATRIC VACCINE 10 micrograms/dose concentrate for dispersion for injection.
THAWING PRIOR TO DILUTION OF COMIRNATY 30 MICROGRAMS/DOSE CONCENTRATE FOR DISPERSION FOR INJECTION (12 YEARS AND OLDER)	
	• The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195-vial pack may take 3 hours to thaw.

<table>
<tr>
<td> 
</td>
<td>Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
• The unopened vial can be stored for up to 1-month at 2 °C to 8 °C not exceeding the printed expiry date (EXP). Within the 1-month shelf-life at 2 °C to 8 °C, up to 48 hours may be used for transportation.
• Allow the thawed vial to come to room temperature. Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.
• Gently invert the vial 10 times prior to dilution. Do not shake.
• Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.</td>
</tr>
<tr>
<td colspan="2">DILUTION OF COMIRNATY 30 MICROGRAMS/DOSE CONCENTRATE FOR DISPERSION FOR INJECTION (12 YEARS AND OLDER)</td>
</tr>
</table>

 **1.8 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.**	• The thawed vaccine must be diluted in its original vial with 1,8 mL sodium chloride 9 mg/mL (0,9 %) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1,8 mL air into the empty diluent syringe.

 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
 **Discard Time** **Record appropriate date and time.** **Use within 6 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution store at 2 ºC to 30 ºC and use within 6 hours, including any transportation time. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.
PREPARATION OF INDIVIDUAL 0,3 mL DOSES OF COMIRNATY 30 MICROGRAMS/DOSE CONCENTRATE FOR DISPERSION FOR INJECTION (12 YEARS AND OLDER)	
	• After dilution, the vial contains 2,25 mL from which 6 doses of 0,3 mL can be extracted.



0,3 mL diluted vaccine

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0,3 mL of COMIRNATY.

  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 microlitres.

  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.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

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