SCHEDULING STATUS: TBC

1. NAME OF THE MEDICINE

COMIRNATY concentrate for dispersion for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COMIRNATY is a multidose vial and must be diluted before use.

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

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

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 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

Individuals 12 years of age and older

COMIRNATY is administered intramuscularly after dilution as a 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).

There are no data available on the interchangeability of COMIRNATY with other COVID-19 vaccines to complete the vaccination course. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the vaccination course.

Special populations

Elderly

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

Paediatric population

The safety and efficacy of COMIRNATY in paediatric participants aged less than 12 years have not yet been established. Limited data are available.

Method of administration

COMIRNATY 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].

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. A second dose of the vaccine 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 in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Medical practitioners should be alert to the signs and symptoms of myocarditis and pericarditis. 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.

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, tingling sensations 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, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY 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

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

There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breastfeeding

It is unknown whether COMIRNATY is excreted in human milk.

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

The safety of COMIRNATY was evaluated in participants 12 years of age and older in 2 clinical studies that included 23,205 participants (comprised of 22,074 participants 16 years of age and older and 1,131 adolescents 12 to 15 years of age) that have received at least one dose of COMIRNATY.

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.

Participants 16 years of age and older

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 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
In an analysis of Study 2, based on data up to the cut-off date of 13 March 2021, 2,260 adolescents (1,131 COMIRNATY and 1,129 placebo) were 12 to 15 years of age. Of these, 1,308 adolescents (660 COMIRNATY and 648 placebo) have been followed for at least 2 months after the second dose of COMIRNATY. The safety evaluation in Study 2 is ongoing.

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

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
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash, pruritus, urticaria[a], angioedema[a])
	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[b]
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[c]
General disorders and administration site conditions	Very common	Injection site pain, fatigue, chills, pyrexia[d], injection site swelling
	Common	Injection site redness

	Uncommon	Asthenia, malaise, injection site pruritus
a. The frequency category for urticaria and angioedema was rare. 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 COVID-19 mRNA vaccine 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. Refers to vaccinated arm. d. A higher frequency of pyrexia was observed after the second dose.		

Post-marketing side effects

Cardiac disorders: Myocarditis, pericarditis

Gastrointestinal disorders: Diarrhoea, vomiting

General disorders and administration site conditions: Extensive swelling of vaccinated limb, facial swelling

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

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**	**Placebo** **N[a] = 18,325**	**Vaccine efficacy % (95 % CI)[fe]**

	Cases **n1[b]** **Surveillance time[c]** **(n2[d])**	**Cases** **n1[b]** **Surveillance time[c]** **(n2[d])**	
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 (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 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 %) 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

In an analysis of Study 2 in adolescents 12 to 15 years of age 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).

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.

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 were 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

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:

6 months at -90 °C to -60 °C.

Within the 6 months 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.

Thawed vial:

1 month at 2 °C to 8 °C.

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.

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.

Thawed vials can be handled in room light conditions.

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

6.5 Nature and contents of container

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).

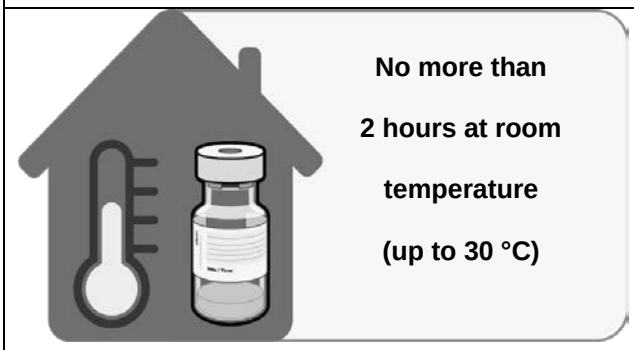
Pack size: 195 vials

6.6 Special precautions for disposal and other handling

Handling instructions

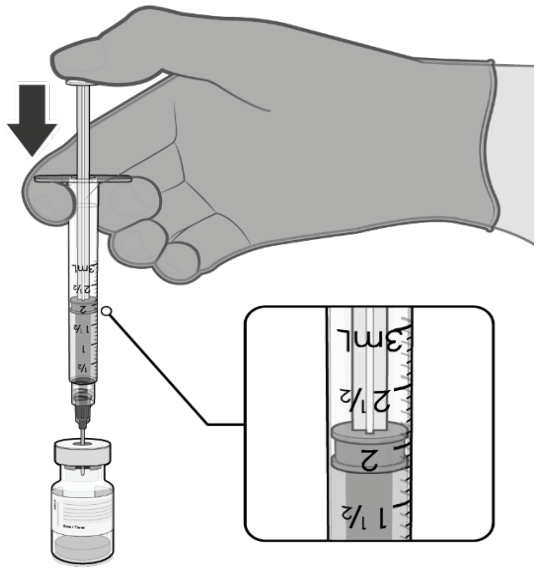
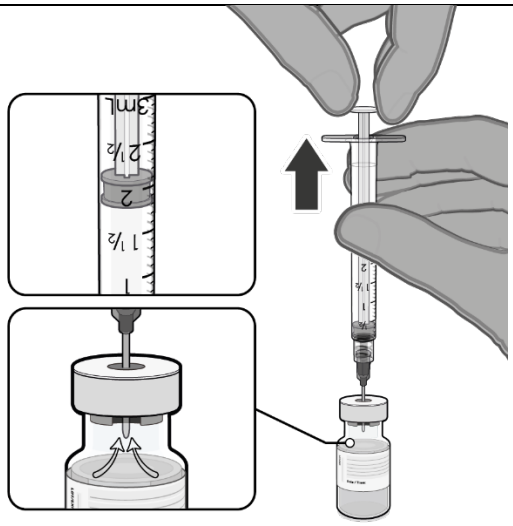
COMIRNATY should be prepared by a health care provider using aseptic technique to ensure the sterility of the prepared dispersion.

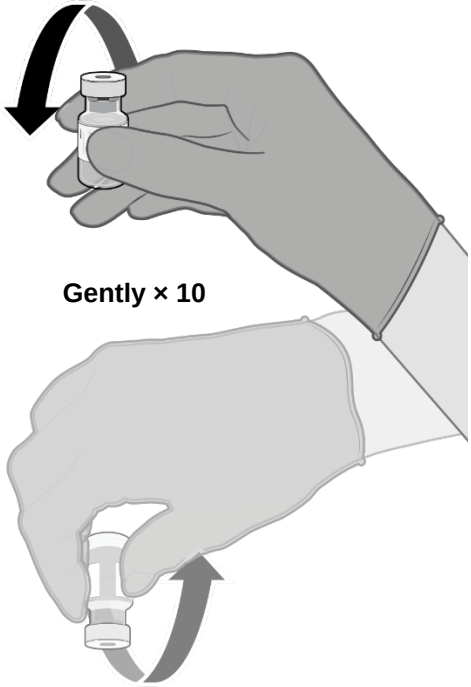
THAWING PRIOR TO DILUTION



- 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. 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. Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.
- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

DILUTION

 **1,8 mL of 0,9 % sodium chloride 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.

<table>
<tr>
<td> 
Gently × 10</td>
<td>

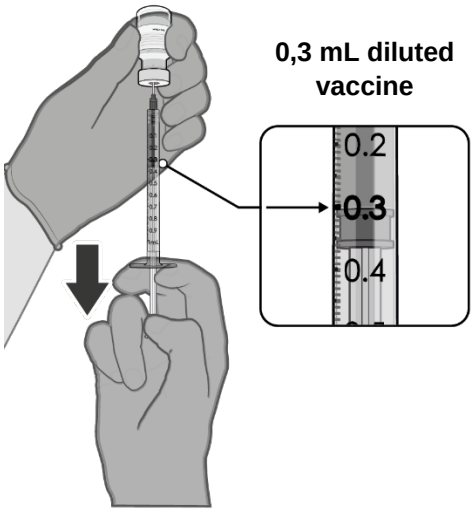
Gently invert the diluted dispersion 10 times. Do not shake.
The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.

</td>
</tr>
<tr>
<td> 

Record appropriate date and time.
Use within 6 hours after dilution</td>
<td>

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.

</td>
</tr>
<tr>
<td colspan="2">PREPARATION OF INDIVIDUAL 0,3 mL DOSES OF COMIRNATY</td>
</tr>
</table>

	• After dilution, the vial contains 2,25 mL from which 6 doses of 0,3 mL can be extracted. • 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

Sandton 2196

South Africa

Tel: +27(0) 11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

To be advised.

9. DATE OF FIRST AUTHORISATION

25 January 2022

10. DATE OF REVISION OF THE TEXT