

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty 30 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial 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.

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 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).

A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available vaccine effectiveness data, taking into account limited safety data (see sections 4.4 and 5.1).

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers to complete the primary vaccination course or the booster dose (third dose) has not been established. Individuals

who have received 1 dose of Comirnaty should receive a second dose of Comirnaty to complete the primary vaccination course and for any additional doses. Doses of Comirnaty 30 micrograms/dose concentrate for dispersion for injection after dilution and Comirnaty 30 micrograms/dose dispersion for injection are considered interchangeable.

Severely immunocompromised aged 12 years and older

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

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.

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 years of age. The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

Method of administration

Comirnaty should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty contain 6 doses of 0.3 mL of vaccine. In order to extract 6 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 medicinal products.

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 the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

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

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.

Healthcare professionals 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.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of Comirnaty has not yet been characterised.

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

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine 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

As with any vaccine, 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

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

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

4.5 Interaction with other medicinal products 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.

Breast-feeding

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 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.

Additionally, 306 existing Phase 3 participants 18 to 55 years of age received a booster dose (third dose) of Comirnaty approximately 6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after 2 doses.

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 of age 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 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 that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 18 years of age and older – after booster dose (third dose)

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 (third dose) of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

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

Tabulated list of adverse reactions from clinical studies and post-authorisation experience 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 ($\geq 1/10$),
- Common ($\geq 1/100$ to $< 1/10$),
- Uncommon ($\geq 1/1,000$ to $< 1/100$),
- Rare ($\geq 1/10,000$ to $< 1/1,000$),
- Very rare ($< 1/10,000$),
- Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 12 years of age and older

| System Organ Class | Very common (≥ 1/10) | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1,000 to < 1/100) | Rare (≥ 1/10,000 to < 1/1,000) | Not known (cannot be estimated from the available data) |
|--|---|--------------------------------------|--|--|--|
| Blood and lymphatic system disorders | | | Lymphadenopathy ^a | | |
| Immune system disorders | | | Hypersensitivity reactions (e.g. rash, pruritus, urticaria, ^b angioedema ^b) | | Anaphylaxis |
| Metabolism and nutrition disorders | | | Decreased appetite | | |
| Psychiatric disorders | | | Insomnia | | |
| Nervous system disorders | Headache | | Lethargy | Acute peripheral facial paralysis ^c | |
| Cardiac disorders | | | | | Myocarditis; ^d Pericarditis ^d |
| Gastrointestinal disorders | Diarrhoea ^d | Nausea; Vomiting ^d | | | |
| Skin and subcutaneous tissue disorder | | | Hyperhidrosis; Night sweats | | |
| Musculoskeletal and connective tissue disorders | Arthralgia; Myalgia | | Pain in extremity ^e | | |
| General disorders and administration site conditions | Injection site pain; Fatigue; Chills; Pyrexia; ^f Injection site swelling | Injection site redness | Asthenia; Malaise; Injection site pruritus | | Extensive swelling of vaccinated limb; ^d Facial swelling ^g |

- A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.
- The frequency category for urticaria and angioedema was Rare.
- 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.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compare to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#) and include batch/Lot number if available.

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 Comirnaty (tozinameran) 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 neutralizing 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 hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (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 products or immunoglobulins within 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/m², 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 n^{1b} Surveillance time^c (n^{2d}) | Placebo N^a = 18,325 Cases n^{1b} Surveillance time^c (n^{2d}) | Vaccine efficacy % (95% CI)^e |
| 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 (3848) | 19 0.511 (3880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3074) | 14 0.406 (3095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

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

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

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- 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 prior SARS-CoV-2 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)* 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 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 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 noninferiority 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 (third dose)

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). 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 summarized in Table 5.

Table 5: SARS-CoV-2 neutralization 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 noninferiority objective (Y/N) |
|---|------------------|--|---|--|------------------------------------|
| Geometric mean 50% neutralizing titer (GMT^b) | 212 ^a | 2466.0 ^b (2202.6, 2760.8) | 750.6 ^b (656.2, 858.6) | 3.29 ^c (2.77, 3.90) | Y ^d |
| Seroresponse rate (%) for 50% neutralizing titer[†] | 200 ^e | 199 ^f 99.5% (97.2%, 100.0%) | 196 ^f 98.0% (95.0%, 99.5%) | 1.5% ^g (-0.7%, 3.7% ^h) | Y ⁱ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean 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 Comirnaty) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

[‡] All eligible participants who had received 2 doses of Comirnaty as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

-
- a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
 - b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
 - c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
 - d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
 - e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
 - f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
 - g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
 - h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
 - i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

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 Comirnaty (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 Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing 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 fetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty 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 medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

Frozen vial

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

Within the 9-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.

Thawed vial

1 month at 2 °C to 8 °C within the 9-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 healthcare professionals 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 medicinal product

Chemical and physical in-use stability, including during transportation, has been demonstrated for 6 hours at 2 °C to 30 °C 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 product 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 medicinal product, 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 purple flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see section 6.6.

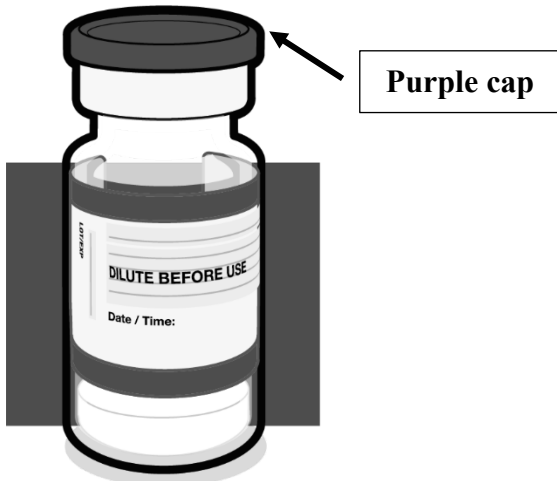
Pack size: 195 vials

6.6 Special precautions for disposal and other handling

Handling instructions

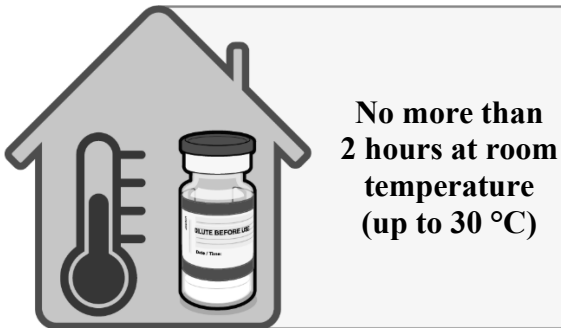
Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

DOSE VERIFICATION



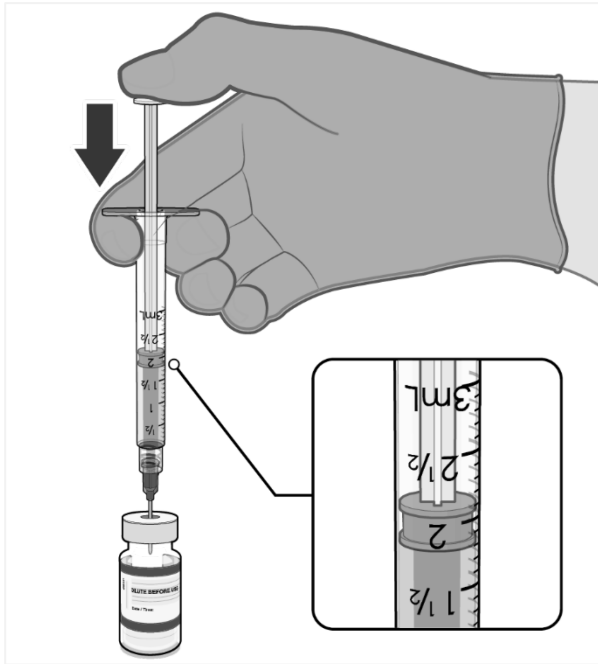
- Verify that the vial has a purple plastic cap. If the vial has a grey plastic cap, please make reference to the Summary of Product Characteristics for Comirnaty 30 micrograms/dose dispersion for injection.

THAWING PRIOR TO DILUTION



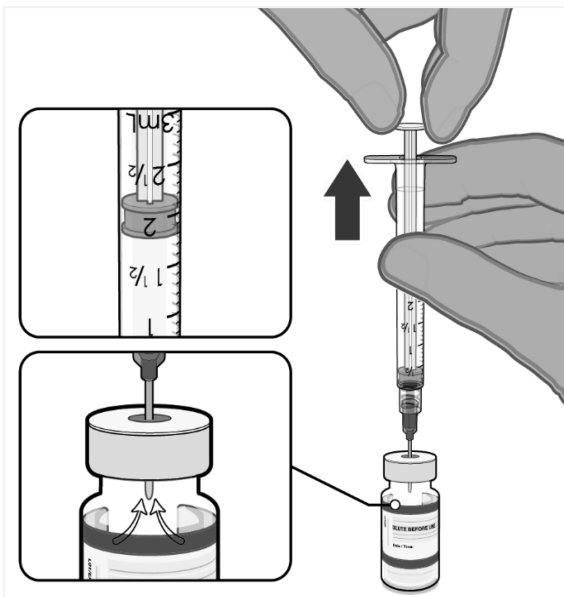
- The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
- The unopened vial can be stored for up to 1 month at 2 °C to 8 °C within the 9-month shelf life. 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. 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.

DILUTION



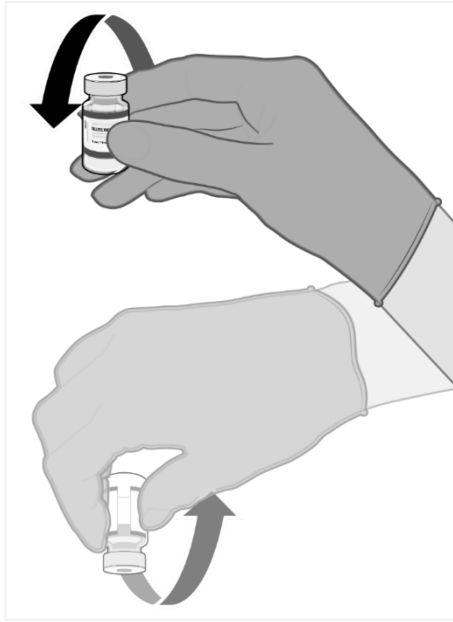
1.8 mL of 0.9% sodium chloride injection

- 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.



Gently × 10

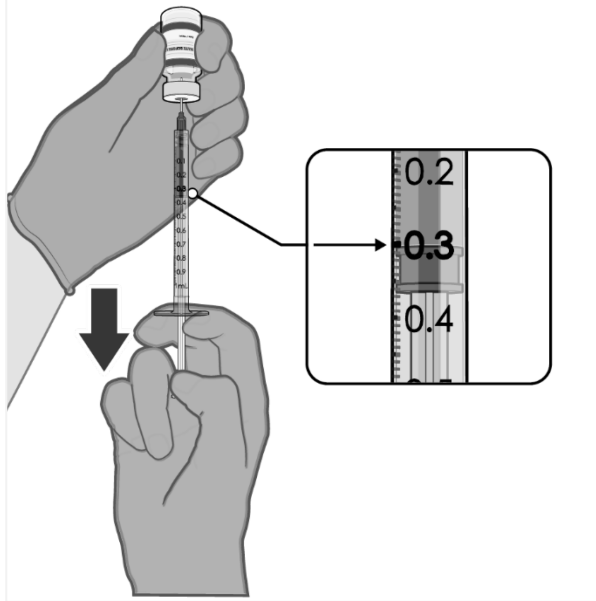
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.



**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 °C to 30 °C 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



0.3 mL diluted vaccine

- 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty 30 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (2.25 mL) contains 6 doses of 0.3 mL, see 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

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 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).

A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Comirnaty should be made based on available vaccine effectiveness data, taking into account limited safety data (see sections 4.4 and 5.1).

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers to complete the primary vaccination course or the booster dose (third dose) has not been established. Individuals

who have received 1 dose of Comirnaty should receive a second dose of Comirnaty to complete the primary vaccination course and for any additional doses. Doses of Comirnaty 30 micrograms/dose concentrate for dispersion for injection after dilution and Comirnaty 30 micrograms/dose dispersion for injection are considered interchangeable.

Severely immunocompromised aged 12 years and older

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

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.

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 years of age. The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

Method of administration

Comirnaty should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

Vials of Comirnaty contain 6 doses of 0.3 mL of vaccine. In order to extract 6 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 medicinal products.

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 the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

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

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.

Healthcare professionals 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.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of Comirnaty has not yet been characterised.

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

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy and safety of the vaccine 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

As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

4.5 Interaction with other medicinal products 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.

Breast-feeding

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 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.

Additionally, 306 existing Phase 3 participants 18 to 55 years of age received a booster dose (third dose) of Comirnaty approximately 6 months after the second dose. The overall safety profile for the booster dose (third dose) was similar to that seen after 2 doses.

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 of age 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 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 that received 2 doses were injection site pain ($> 90\%$), fatigue and headache ($> 70\%$), myalgia and chills ($> 40\%$), arthralgia and pyrexia ($> 20\%$).

Participants 18 years of age and older – after booster dose (third dose)

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 (third dose) of Comirnaty approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

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

Tabulated list of adverse reactions from clinical studies and post-authorisation experience 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 ($\geq 1/10$),
- Common ($\geq 1/100$ to $< 1/10$),
- Uncommon ($\geq 1/1,000$ to $< 1/100$),
- Rare ($\geq 1/10,000$ to $< 1/1,000$),
- Very rare ($< 1/10,000$),
- Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 12 years of age and older

| System Organ Class | Very common (≥ 1/10) | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1,000 to < 1/100) | Rare (≥ 1/10,000 to < 1/1,000) | Not known (cannot be estimated from the available data) |
|--|---|--|--|--|---|
| Blood and lymphatic system disorders | | | Lymphadenopathy ^a | | |
| Immune system disorders | | | Hypersensitivity reactions (e.g. rash, pruritus, urticaria, ^b angioedema ^b) | | Anaphylaxis |
| Metabolism and nutrition disorders | | | Decreased appetite | | |
| Psychiatric disorders | | | Insomnia | | |
| Nervous system disorders | Headache | | Lethargy | Acute peripheral facial paralysis ^c | |
| Cardiac disorders | | | | | Myocarditis; ^d Pericarditis ^d |
| Gastrointestinal disorders | Diarrhoea ^d | Nausea; Vomiting ^d | | | |
| Skin and subcutaneous tissue disorder | | | Hyperhidrosis; Night sweats | | |
| Musculoskeletal and connective tissue disorders | Arthralgia; Myalgia | | Pain in extremity ^e | | |
| General disorders and administration site conditions | Injection site pain; Fatigue; Chills; Pyrexia; ^f Injection site swelling | Injection site redness | Asthenia; Malaise; Injection site pruritus | | Extensive swelling of vaccinated limb; ^d Facial swelling ^g |

- A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses.
- The frequency category for urticaria and angioedema was Rare.
- 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.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compare to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#) and include batch/Lot number if available.

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 Comirnaty (tozinameran) 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 neutralizing 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 hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (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 products or immunoglobulins within 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/m², 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)^e |
| 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 (3848) | 19 0.511 (3880) | 94.7 (66.7, 99.9) |
| 65 to 74 years | 1 0.406 (3074) | 14 0.406 (3095) | 92.9 (53.1, 99.8) |
| 75 years and older | 0 0.102 (774) | 5 0.106 (785) | 100.0 (-13.1, 100.0) |

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

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

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- 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 prior SARS-CoV-2 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- 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)* 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 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 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 noninferiority 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 (third dose)

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). 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 summarized in Table 5.

Table 5: SARS-CoV-2 neutralization 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 noninferiority objective (Y/N) |
|---|------------------|--|---|--|------------------------------------|
| Geometric mean 50% neutralizing titer (GMT^b) | 212 ^a | 2466.0 ^b (2202.6, 2760.8) | 750.6 ^b (656.2, 858.6) | 3.29 ^c (2.77, 3.90) | Y ^d |
| Seroresponse rate (%) for 50% neutralizing titer[†] | 200 ^e | 199 ^f 99.5% (97.2%, 100.0%) | 196 ^f 98.0% (95.0%, 99.5%) | 1.5% ^g (-0.7%, 3.7% ^h) | Y ⁱ |

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean 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 Comirnaty) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

[‡] All eligible participants who had received 2 doses of Comirnaty as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Comirnaty, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

-
- a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
 - b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
 - c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
 - d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .
 - e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
 - f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
 - g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
 - h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
 - i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

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 Comirnaty (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 Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing 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 Comirnaty 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

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

Frozen vial

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

The vaccine may be received frozen at -90 °C to -60 °C or at -25 °C to -15 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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

Thawed vial

10 weeks storage and transportation at 2 °C to 8 °C within the 6-month shelf life.

- Upon moving the product to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

Opened vial

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. 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 first opening, see section 6.3.

6.5 Nature and contents of container

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

Pack sizes: 195 vials or 10 vials

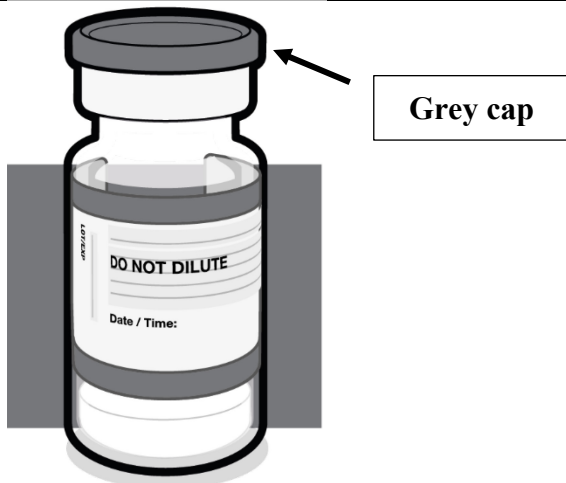
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions

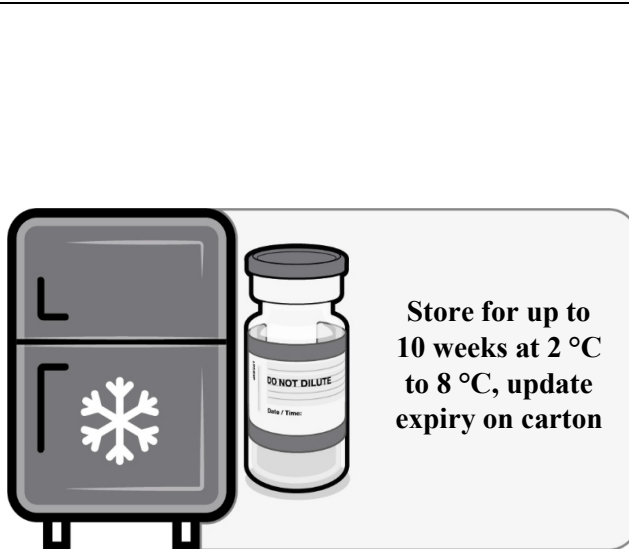
Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

DOSE VERIFICATION

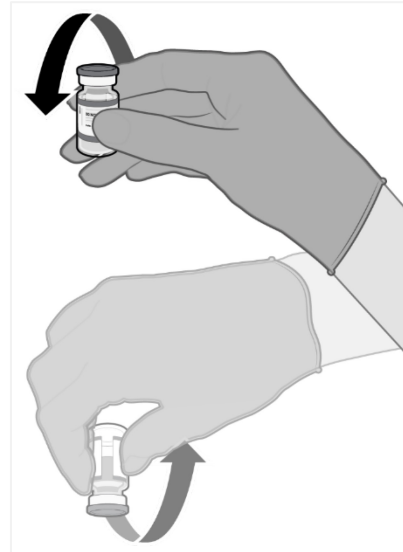


- Verify that the vial has a grey plastic cap. If the vial has a purple plastic cap, please make reference to the Summary of Product Characteristics for Comirnaty 30 micrograms/dose concentrate for dispersion for injection.

HANDLING PRIOR TO USE



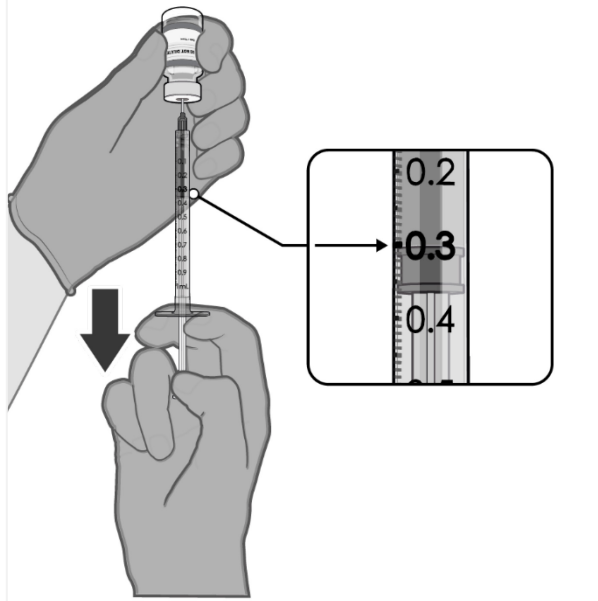
- If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 6 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C within the 6-month shelf life.
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.



Gently × 10

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

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY



0.3 mL 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 12 hours after first puncture. Record the appropriate date/time on the vial.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/003
EU/1/20/1528/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance(s)

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany

BioNTech Manufacturing Marburg GmbH
Emil-von-Behring-Strasse 76
35401 Marburg
Germany

Rentschler Biopharma SE
Erwin-Rentschler-Strasse 21
88471 Laupheim
Germany

Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC
1 Burt Road
Andover, MA 01810
USA

Name and address of the manufacturers responsible for batch release

BioNTech Manufacturing GmbH
Kupferbergterrasse 17 - 19
55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

• **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data. | July 2021. Interim reports: 31 March 2021 |
| In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications. | July 2021. Interim reports: March 2021 |
| In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. | July 2021. Interim reports: January 2021, April 2021 |
| In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159. | July 2021. Interim reports: January 2021, April 2021 |

| Description | Due date |
|--|-----------------|
| In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001. | December 2023 |

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX LABEL

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 30 micrograms/dose concentrate for dispersion for injection
Adults and adolescents from 12 years
COVID-19 mRNA Vaccine (nucleoside modified)
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.

Scan QR code for more information.

Dilute before use: Dilute each vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 1 month. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Storage:

Prior to dilution, store at -90 °C to -60 °C in the original package in order to protect from light.
After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 30 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 doses of 30 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 30 micrograms/dose dispersion for injection
Adults and adolescents from 12 years
COVID-19 mRNA Vaccine (nucleoside modified)
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
195 multidose vials
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use

Scan QR code for more information.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out the former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Storage:

Store at 2 °C to 8 °C after receipt. Do not refreeze once thawed.

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

Read the package leaflet before use and for additional storage information.

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/003 195 multidose vials

EU/1/20/1528/002 10 multidose vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 30 mcg injection
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 doses of 30 mcg

6. OTHER

Discard time:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comirnaty 30 micrograms/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before you receive Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.

Comirnaty is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

2. What you need to know before you receive Comirnaty

Comirnaty should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given Comirnaty in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with Comirnaty. The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

You may receive a third dose of Comirnaty. The third dose may still not provide full immunity to COVID-19 in people who are immunocompromised. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty is not recommended for children aged under 12 years.

Other medicines and Comirnaty

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

Comirnaty contains potassium and sodium

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

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

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 2 injections.

It is recommended to receive the second dose of the same vaccine 3 weeks after the first dose to complete the vaccination course.

A booster dose (third dose) of Comirnaty may be given at least 6 months after the second dose in individuals 18 years of age and older.

If you are immunocompromised, you may receive a third dose of Comirnaty at least 28 days after the second dose.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness
- headache
- muscle pain
- chills
- joint pain
- diarrhoea
- fever

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea
- vomiting

Uncommon side effects: may affect up to 1 in 100 people

- enlarged lymph nodes (more frequently observed after the booster dose)
- feeling unwell
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- feeling weak or lack of energy/sleepy
- decreased appetite
- excessive sweating
- night sweats

Rare side effects: may affect up to 1 in 1,000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Not known (cannot be estimated from the available data)

- severe allergic reaction
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$. Within the 9-month shelf life unopened vials may be stored and transported at $-25\text{ }^{\circ}\text{C}$ to $-15\text{ }^{\circ}\text{C}$ for a single period of up to 2 weeks and can be returned to $-90\text{ }^{\circ}\text{C}$ to $-60\text{ }^{\circ}\text{C}$.

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

Transfers of frozen vials stored at ultra-low temperature ($< -60\text{ }^{\circ}\text{C}$)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage ($< -60\text{ }^{\circ}\text{C}$) may be at temperatures up to $25\text{ }^{\circ}\text{C}$ for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage ($< -60\text{ }^{\circ}\text{C}$) may be at temperatures up to $25\text{ }^{\circ}\text{C}$ for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to $25\text{ }^{\circ}\text{C}$, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at $-25\text{ }^{\circ}\text{C}$ to $-15\text{ }^{\circ}\text{C}$

- Closed-lid vial trays containing 195 vials removed from frozen storage ($-25\text{ }^{\circ}\text{C}$ to $-15\text{ }^{\circ}\text{C}$) may be at temperatures up to $25\text{ }^{\circ}\text{C}$ for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage ($-25\text{ }^{\circ}\text{C}$ to $-15\text{ }^{\circ}\text{C}$) may be at temperatures up to $25\text{ }^{\circ}\text{C}$ for up to 1 minute.

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

After thawing, the vaccine should be diluted and used immediately. However, in-use stability data have demonstrated that once removed from freezer, the undiluted vaccine can be stored for up to 1 month at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$ within the 9-month shelf life. Within the 1-month shelf life at $2\text{ }^{\circ}\text{C}$ to $8\text{ }^{\circ}\text{C}$, up to 12 hours may be used for transportation. Prior to use, the unopened vaccine can be stored for up to 2 hours at temperatures up to $30\text{ }^{\circ}\text{C}$.

Thawed vials can be handled in room light conditions.

After dilution, store and transport the vaccine at $2\text{ }^{\circ}\text{C}$ to $30\text{ }^{\circ}\text{C}$ and use within 6 hours. Discard any unused vaccine.

Once removed from the freezer and diluted, the vials should be marked with the new discard date and time. Once thawed, the vaccine cannot be re-frozen.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance is COVID-19 mRNA Vaccine called tozinameran. After dilution, the vial contains 6 doses of 0.3 mL with 30 micrograms tozinameran each.
- The other ingredients are:
 - ((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

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a purple flip-off plastic cap with aluminium seal.

Pack size: 195 vials

Marketing Authorisation Holder

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

Manufacturers

BioNTech Manufacturing GmbH
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55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Pfizer S.A./N.V.
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Nederland

Pfizer BV
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Österreich

Pfizer Corporation Austria Ges.m.b.H
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Pfizer Polska Sp. z o.o.
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Laboratórios Pfizer, Lda.
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România

Pfizer Romania S.R.L
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Pfizer, podružnica za svetovanje s področja
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Sverige

Pfizer AB
Tel: +46 (0)8 550 520 00

United Kingdom (Northern Ireland)

Pfizer Limited
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Latvija

Pfizer Luxembourg SARL filiāle Latvijā

Tel.: +371 670 35 775

This leaflet was last revised in {MM/YYYY}

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>.

This package leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly after dilution as a primary course of 2 doses (0.3 mL each) 3 weeks apart. A booster dose (third dose) of Comirnaty may be given at least 6 months after the second dose in individuals 18 years of age and older.

A third dose may be given at least 28 days after the second dose to individuals who are severely immunocompromised.

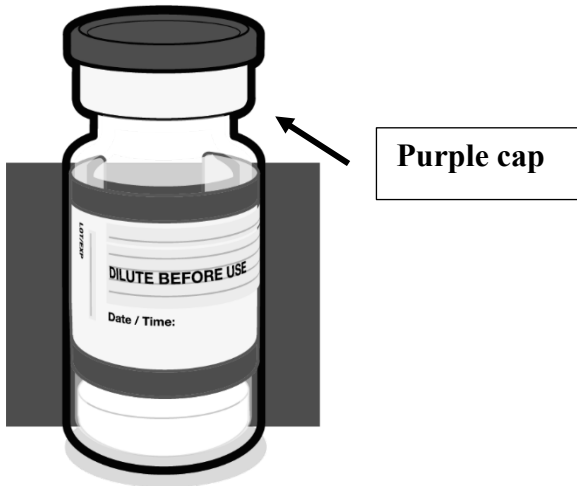
Traceability

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

Handling instructions

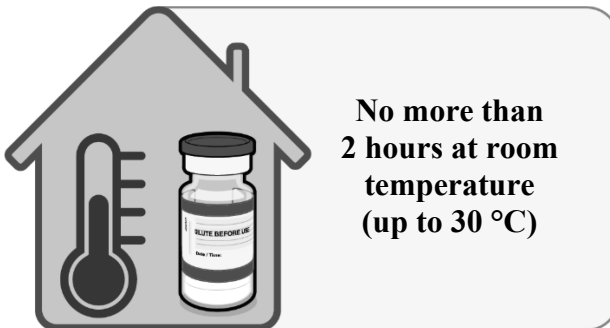
Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

DOSE VERIFICATION



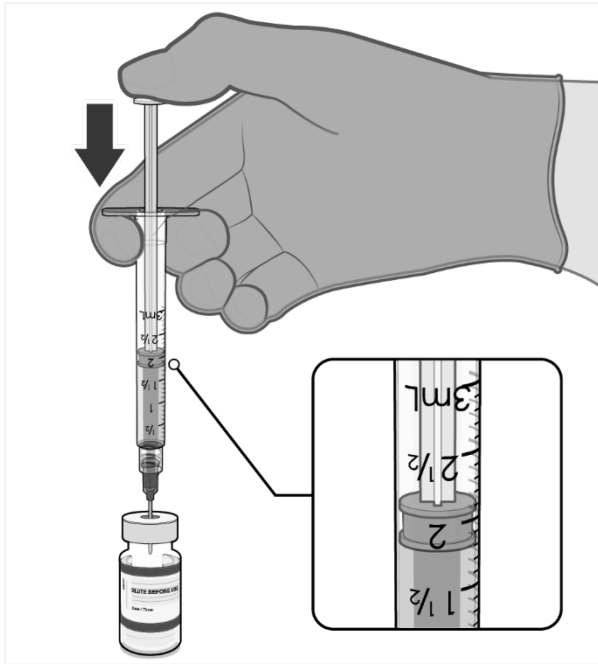
- Verify that the vial has a purple plastic cap. If the vial has a grey plastic cap, please make reference to the Summary of Product Characteristics for Comirnaty 30 micrograms/dose dispersion for injection.

THAWING PRIOR TO DILUTION



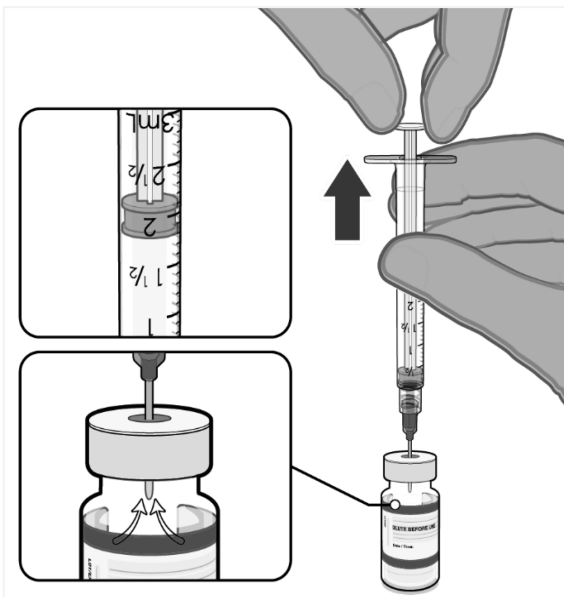
- The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
- The unopened vial can be stored for up to 1 month at 2 °C to 8 °C within the 9-month shelf life. 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. 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.

DILUTION



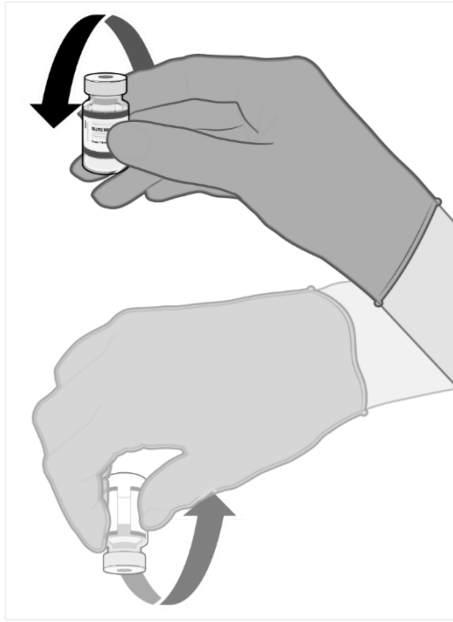
1.8 mL of 0.9% sodium chloride injection

- 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.



Gently × 10

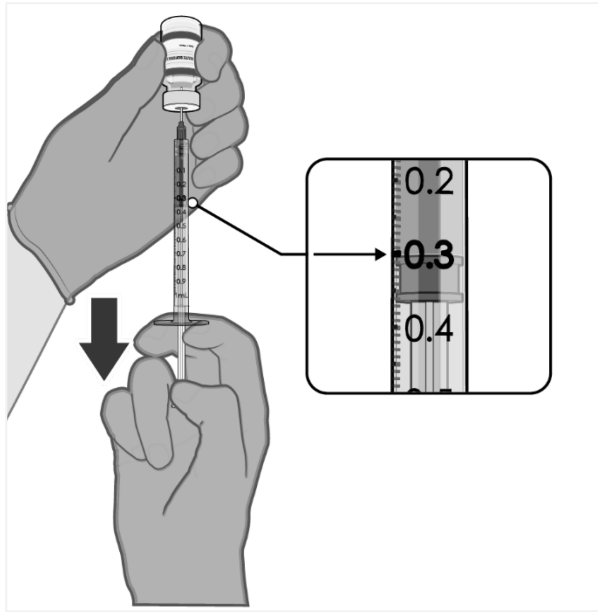
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.



**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 °C to 30 °C 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



0.3 mL diluted vaccine

- 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 medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty 30 micrograms/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine (nucleoside modified) tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before you receive Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.

Comirnaty is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

2. What you need to know before you receive Comirnaty

Comirnaty should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given Comirnaty in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with Comirnaty. The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

You may receive a third dose of Comirnaty. The third dose may still not provide full immunity to COVID-19 in people who are immunocompromised. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty is not recommended for children aged under 12 years.

Other medicines and Comirnaty

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty is given

Comirnaty is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 2 injections.

It is recommended to receive the second dose of the same vaccine 3 weeks after the first dose to complete the vaccination course.

A booster dose (third dose) of Comirnaty may be given at least 6 months after the second dose in individuals 18 years of age and older.

If you are immunocompromised, you may receive a third dose of Comirnaty at least 28 days after the second dose.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness
- headache
- muscle pain
- chills
- joint pain
- diarrhoea
- fever

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea
- vomiting

Uncommon side effects: may affect up to 1 in 100 people

- enlarged lymph nodes (more frequently observed after the booster dose)
- feeling unwell
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- feeling weak or lack of energy/sleepy
- decreased appetite
- excessive sweating
- night sweats

Rare side effects: may affect up to 1 in 1,000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Not known (cannot be estimated from the available data)

- severe allergic reaction
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C for 6 months.

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

The vaccine may be received frozen at -90 °C to -60 °C or at -25 °C to -15 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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

Once removed from the freezer, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks within the 6-month shelf life. The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

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

Thawed vials can be handled in room light conditions.

After first puncture, store and transport the vaccine at 2 °C to 30 °C and use within 12 hours. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance is COVID-19 mRNA Vaccine called tozinameran. The vial contains 6 doses of 0.3 mL with 30 micrograms tozinameran each.
- The other ingredients are:
 - ((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
 - trometamol
 - trometamol hydrochloride
 - sucrose
 - water for injections

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Pack sizes: 195 vials or 10 vials

Not all pack sizes may be marketed.

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This leaflet was last revised in {MM/YYYY}

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>.

This package leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly as a primary course of 2 doses (0.3 mL each) 3 weeks apart. A booster dose (third dose) of Comirnaty may be given at least 6 months after the second dose in individuals 18 years of age and older.

A third dose may be given at least 28 days after the second dose to individuals who are severely immunocompromised.

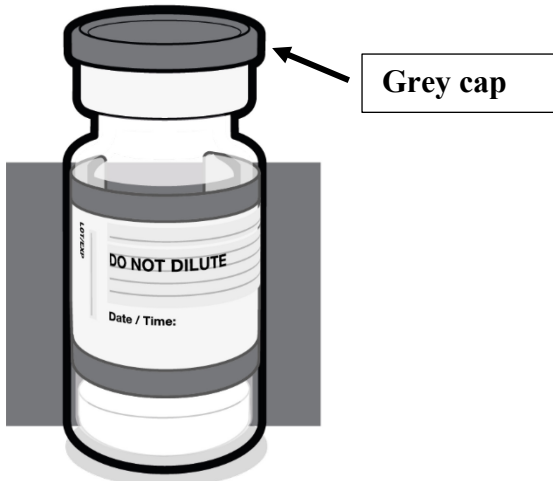
Traceability

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

Handling instructions

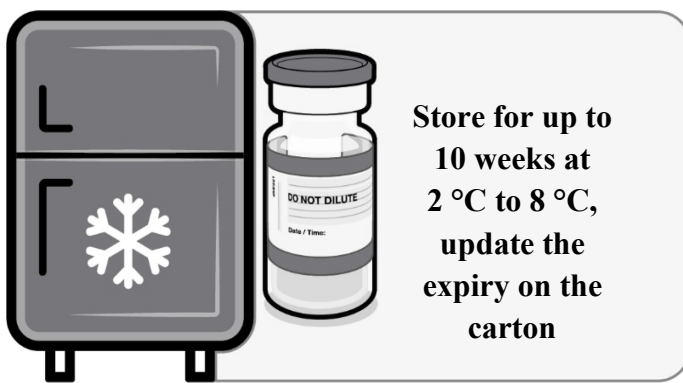
Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

DOSE VERIFICATION

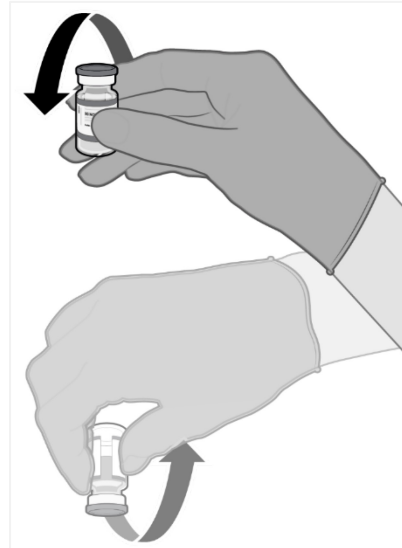


- Verify that the vial has a grey plastic cap. If the vial has a purple plastic cap, please make reference to the Summary of Product Characteristics for Comirnaty concentrate for dispersion for injection.

HANDLING PRIOR TO USE



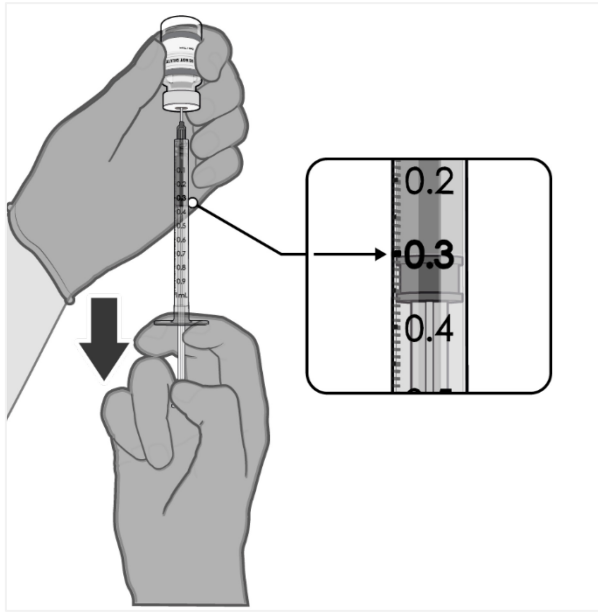
- If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 6 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C within in the 6-month shelf life.
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C. Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.



Gently x 10

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

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY



0.3 mL 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 12 hours after first puncture. Record the appropriate date/time on the vial.

Disposal

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