14 October 2021
EMA/594686/2021
Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report on group of an extension of marketing authorisation and variations

COMIRNATY

International non-proprietary name, Common name: tozinameran, COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/X/0044/G

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

# Administrative information

| | |
|---|---|
| Name of the medicinal product: | COMIRNATY |
| MAH: | BioNTech Manufacturing GmbH<br>An der Goldgrube 12<br>55131 Mainz<br>GERMANY |
| Active substance: | Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 |
| International Non-proprietary Name/ Common Name: | tozinameran<br>COVID-19 mRNA vaccine (nucleoside-modified) |
| Pharmaco-therapeutic group (ATC Code): | viral vaccines, other viral vaccines (J07BX03) |
| Therapeutic indication(s): | Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.<br>The use of this vaccine should be in accordance with official recommendations. |
| Pharmaceutical form(s): | Concentrate for dispersion for injection;<br>Dispersion for injection |
| Strength(s): | -- |
| Route(s) of administration: | Intramuscular use |
| Packaging: | vial (glass) |
| Package size(s): | 10 multidose vials (60 doses) and 195 multidose vials (1170 doses) |

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# List of abbreviations

| | |
|---|---|
| ALC-0159 | PEG-lipid, 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide |
| ALC-0315 | Cationic lipid, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) |
| BNT162b2 | Vaccine candidate encoding the SARS-CoV-2 full-length spike protein, modified by 2 proline mutations (P2 S) |
| BSE | bovine spongiform encephalopathies |
| CAD | Charged Aerosol Detection |
| CCI | Container Closure Integrity |
| CMA | Conditional marketing authorization |
| COVID-19 | Coronavirus disease 2019 |
| ddPCR | Droplet digital PCR |
| DSPC | Phospholipid, (1,2-distearoyl-sn-glycero-3-phosphocholine) |
| HPLC | High Performance Liquid Chromatography |
| ICH | International Council for Harmonisation |
| IR | Infrared spectroscopy |
| IVE | In-Vitro Expression |
| LNP | Lipid nanoparticle |
| mRNA | Messenger RNA |
| NMR | Nuclear Magnetic Resonance |
| PBS | Phosphate-Buffered Saline |
| PCR | Polymerase Chain Reaction |
| PEG | Polyethylene glycol |
| Ph. Eur. | European Pharmacopeia |
| poly(A) | polyadenosine |
| PPQ | Process Performance Qualification |
| QTPP | Quality Target Product Profile |
| RP-HPLC | ion-pair reversed-phase high performance liquid chromatography |
| RR | Rolling review |
| RT-PCR | Reverse Transcription Polymerase Chain Reaction |

| | |
|---|---|
| SARS | Severe acute respiratory syndrome |
| SARS-CoV-2 | SARS Coronavirus-2; virus causing the disease COVID-19 |
| TFF | Tangential Flow Filtration |
| Tris | Tromethamine |
| Tris HCl | (Hydroxymethyl) aminomethane hydrochloride |
| TSE | transmitting transmissible spongiform encephalopathies |
| USP | United States Pharmacopeia |
| UV | Ultraviolet |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

BioNTech Manufacturing GmbH submitted on 17 June 2021 a group of variations consisting of an extension of the marketing authorisation and the following variations:

| **Variations requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| X.02.III | Annex I_2.(c) Change or addition of a new strength/potency | Line Extension | I, IIIA, IIIB and A |
| X.02.IV | Annex I_2.(d) Change or addition of a new pharmaceutical form | Line Extension | I, IIIA, IIIB and A |
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | IB | I |
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | IB | IIIA |
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | IB | I, IIIA and IIIB |
| A.3 | A.3 - Administrative change - Change in name of the AS or of an excipient | IAin | I, IIIA and IIIB |

- Extension application to add a new pharmaceutical form (dispersion for injection) with a new strength (0.1 mg/ml).
- To update sections 6.4, 6.5 and 6.6 of the SmPC, section 5, 6 and information for healthcare professionals of the PL, section 1 of the Carton Box Label as well as section 1 and 5 of the Vial Label to ensure the correct handling by providing dose verification information about strength, age range, colour information of the flip-off plastic cap and greyscale images.
- To update sections 4.2 of the SmPC ensure the correct handling in accordance to interchangeability of the medicinal product.
- To update section 8 of Carton Box Label to clarify expiry date "EXP" by adding storage temperature "(at -90°C to -60°C)" to ensure the correct handling of the medicinal product.
- To change the name of the active substance from COVID-19 mRNA Vaccine (nucleoside modified) to Tozinameran.
  The marketing authorisation holder has taken the opportunity to implement minor editorial changes.

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008 - Extensions of marketing authorisations.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations.

## *1.3. Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0396/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0396/2021 was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *1.5. Scientific advice*

The MAH received Scientific Advice from the CHMP on 29 March 2021 (EMA/SA/0000056423). The Scientific Advice pertained to the following quality and regulatory aspects:

- Concurrence that the line extension application for the RTU formulation can be based on analytical comparability without the need for additional non-clinical and clinical studies.
- Labelling issues.
- Rolling review and accelerated timelines for the line extension.

## *1.6. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

| **Rolling Review (RR1)** | Date |
|---|---|
| The first rolling review application (RR1) was received by the EMA on | 16 June 2021 |
| The procedure (RR1) started on | 18 June 2021 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP members on | 5 July 2021 |

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|---|---|
| The CHMP Co-Rapporteur's Critique was circulated to all CHMP members on | 6 July 2021 |
| The assessment report and draft list of questions was discussed by BWP on | 12 July 2021 |
| The CHMP Rapporteurs circulated the updated Assessment Report the consolidated List of Questions to all CHMP members on | 14 July 2021 |
| The CHMP adopted an Interim Opinion and the consolidated List of Questions to be sent to the MAH in writing on | 19 July 2021 |
| **Line Extension (RR2)** | |
| The MAH submitted the line extension and grouped variation application including additional data on quality, RMP and responses to the CHMP consolidated List of Questions on | 21 September 2021 |
| The procedure started on | 23 September 2021 |
| The CHMP Rapporteurs circulated their updated Assessment Report on the additional data and on responses to the List of Questions to all CHMP and PRAC members on | 4 October 2021 |
| The CHMP Co-Rapporteur's Critique was circulated to all CHMP members on | 5 October 2021 |
| The PRAC Rapporteurs circulated their Assessment Report on the RMP to all CHMP and PRAC members on | 5 October 2021 |
| The updated Assessment Report and draft List of Outstanding Issues was discussed by BWP on | 6 October 2021 |
| The MAH submitted the responses to the draft List of Outstanding Issues on | 11 October 2021 |
| The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 11 October 2021 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 14 October 2021 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to COMIRNATY on | 14 October 2021 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

COVID-19 is the respiratory disease caused by the coronavirus SARS-CoV2. The virus first emerged as a human pathogen in Wuhan province in China and has spread world-wide causing a pandemic. The WHO declared the COVID-19 outbreak as a pandemic in March 2020. The virus infects the airways and causes a broad spectrum of respiratory infection from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS).

BNT162b2 is intended for active immunisation against SARS CoV-2, thereby preventing Covid-19.

### 2.1.2. Epidemiology and risk factors

The COVID-19 pandemic puts virtually the entire global population at risk of infection as there is no pre-existing immunity to the SARS-CoV2 virus. Following infection some but not all individuals develop protective immunity in terms of neutralising antibody responses and cell mediated immunity. However, it is currently unknown to what extent and how long this protection lasts.

According to the WHO 80% of infected individuals recover without need for hospital care, while 15% develop more severe disease and 5% need intensive care.

Increasing age and underlying medical conditions are considered risk factors for developing severe disease.

### 2.1.3. Aetiology and pathogenesis

The SARS-CoV2 virus has been circulating globally since 2020. It first emerged as a human pathogen in Wuhan, China. Like other coronaviruses it is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development. It has been shown that antibodies to the Spike protein neutralises the virus and prevents infection.

## *2.2. About the product*

This line extension (EMEA/H/C/005735/X/0044/G) concerns the addition of a new strength and pharmaceutical form of Comirnaty (referred to as the 'Ready-To-Use' or 'Tris-Sucrose' formulation) grouped with a number of minor variations to update the product information of the currently authorised Comirnaty concentrate for dispersion for injection (referred to as 'PBS-Sucrose' formulation) and to introduce the INN 'Tozinameran' to the product information of Comirnaty.

The precise scope of this application is as follows:

- Extension application to add a new pharmaceutical form (dispersion for injection) with a new strength (0.1 mg/ml).

- To update sections 6.4, 6.5 and 6.6 of the SmPC, section 5, 6 and information for healthcare professionals of the PL, section 1 of the Carton Box Label as well as section 1 and 5 of the Vial Label to ensure the correct handling by providing dose verification information about strength, age range, colour information of the flip-off plastic cap and greyscale images.
- To update sections 4.2 of the SmPC ensure the correct handling in accordance to interchangeability of the medicinal product.
- To update section 8 of Carton Box Label to clarify expiry date "EXP" by adding storage temperature "(at -90°C to -60°C)" to ensure the correct handling of the medicinal product.
- To change the name of the active substance from COVID-19 mRNA Vaccine (nucleoside modified) to Tozinameran.

The marketing authorisation holder has taken the opportunity to implement minor editorial changes.

The new Ready-to-Use (RTU) formulation is based on the current approved vaccine except that:

- The formulation buffer has been changed from phosphate buffered saline to Tris buffer without sodium chloride and potassium chloride while maintaining the same target pH.
- The RNA concentration is lower.
- The finished product does not require dilution for administration.

There are no changes to the active substance, or the lipids used to produce the lipid nanoparticles (LNPs) in the bulk finished product.

Both the applied RTU formulation (Tris/Sucrose finished product) and the approved concentrate (PBS/Sucrose finished product) are administered intramuscularly (IM), 30 µg doses (0.3 mL).

The application strategy is summarised in Table 1 below. The Process Performance Qualification (PPQ) strategy has changed from the strategy initially proposed. A network PPQ strategy with PPQ lots from both Puurs and Kalamazoo was initially proposed, however this strategy was revised to separate Puurs and Kalamazoo in two phases. The initial strategy was to provide data in this Roll 2 from 2 PPQ runs at Puurs with 2.25 mL vial filling (30 µg doses) and 1 PPQ run at Puurs filled at 1.3 mL and 0.4 mL (10 and 3 µg doses, respectively for future paediatric use). However, a revised strategy was executed providing 3 PPQ runs with 2.25 mL vial filling.

The current strategy, completed with this Roll 2 submission, is to provide the data from 3 PPQ lots from Puurs filled at 2.25 mL per vial. A separate variation will subsequently provide the data from 3 PPQ lots from Kalamazoo also filled at 2.25 mL per vial, to support registration of Kalamazoo as an additional site of manufacture of the finished product.

**Table 1** ***Network PPQ strategies for Tris/Sucrose formulation.***

| Formulation | Submission | Submission strategy |
|---|---|---|
| Tris/Sucrose 30 µg, roll 1 | June 2021 | Batch analysis, comparability and stability data (1 month) for 3 primary finished product lots (manufactured by Pfizer Puurs at 7-17% commercial scale and representative of the commercial manufacturing process). |

| | | |
|---|---|---|
| Tris/Sucrose 30 µg, roll 2 (Line Extension) | September 2021 | Batch analysis, comparability, process validation for 3 PPQ lots from Pfizer Puurs.<br>Stability data for 3 primary finished product lots (3 months) and 3 PPQ lots (1 month).<br>Product information |
| Tris/Sucrose 10 µg (paediatrics, Line Extension planned) | October 2021 | Line extension application for paediatric formulation. |
| Tris/Sucrose 30 µg (post-approval, variation planned) | November 2021 | Complete data for 3 PPQ lots manufactured by Pfizer Kalamazoo, fill volume 2.25 ml. |

## *2.3. Type of Application and aspects on development*

***Legal basis***

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008 - Extensions of marketing authorisations.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations.

***Accelerated assessment***

The submission of the application is foreseen for accelerated assessment and is submitted as a so-called "rolling submission", see Table 1 above.

***Conditional marketing authorisation***

Comirnaty received a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive. In the final efficacy analysis of Phase 2/3 data, among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, vaccine efficacy (VE) against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. Overall, based on Phase 3 data from approximately 38,000 participants with a median of 2 months of follow-up after Dose2 in Study C4591001, BNT162b2 at 30 µg was safe and well-tolerated in participants ≥16 years of age.
- It is likely that the applicant will be able to provide comprehensive data. COMIRNATY has shown efficacy in the pivotal clinical study. Collecting and understanding vaccine effectiveness once it is available for use in a broader population in the real-world will, in conjunction with long-term real-

world safety surveillance of vaccinees, provide information that can be used to conduct a more informed determination of risk-benefit for vaccination in various sub-populations.

- Unmet medical needs will be addressed, as there have been, over 66 million cases and >1,524,000 deaths worldwide as of 5 December 2020. There are currently no vaccines or antiviral drugs approved in EU Member States (except UK) to prevent or treat SARS-CoV-2 infections or its associated disease COVID-19
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. COVID-19 is a serious and potentially fatal or life-threatening human infection. Efficacy of COMIRNATY to prevent COVID- 19 was overwhelmingly demonstrated at the final analysis of 170 cases, with a VE of 95%. Potential risks include mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations or safety concerns.

## *2.4. Quality aspects*

### 2.4.1. Introduction

The vaccine contains the SARS CoV-2 spike glycoprotein (S) encoded in RNA and formulated in lipid nanoparticles (LNPs). The INN of the active substance is tozinameran, and the common name is COVID-19 mRNA Vaccine (nucleoside modified). It is also referred to throughout the application as COVID-19 Vaccine (BNT162b2).

The Tris/Sucrose finished product is a preservative-free, sterile dispersion of LNPs in an aqueous cryoprotectant buffer for intramuscular administration. It is formulated at 0.1 mg/mL RNA and administered without dilution. One dose (0.3 mL) contains 30 micrograms of tozinameran. This Line Extension submission is for a (6-dose) multi-dose vial only.*

Other ingredients are: ALC-0315((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), cholesterol, sucrose, trometamol (Tris), trometamol hydrochloride and water.

The product is available in glass vial (Type 1 borosilicate glass or aluminosilicate glass) sealed with a bromobutyl rubber stopper and an aluminium seal with flip-off plastic cap, in pack sizes of 195 vials or 10 vials.

*a single dose vial is planned in future but not included in this current submission.

### 2.4.2. Active Substance

The active substance used to manufacture the Tris/Sucrose finished product is identical to that used for the currently approved PBS/Sucrose finished product. The same active substance manufacturing sites are used for both products. Consequently, there are no changes to the active substance sections and full reference is made to the active substance data of Comirnaty, concentrate for dispersion for injection, (EMEA/H/C/005735).

A Type IA variation is submitted to change the name of the active substance from 'COVID-19 mRNA Vaccine (nucleoside modified)' to the approved INN 'Tozinameran'. The variation is considered approvable for the currently authorised product. This line extension and future extension / variation applications will use the approved INN when referring to the active substance. The product information has been updated accordingly.

## 2.4.3. Finished Medicinal Product – (0.1 mg/ml) dispersion for injection

### *2.4.3.1. Description of the product and pharmaceutical development*

The finished product is a preservative-free, sterile dispersion of RNA-containing lipid nanoparticles in an aqueous cryoprotectant buffer for intramuscular injection. The finished product is a multidose vial presentation, containing 2.25 mL, intended for 6 doses. No overages are applied to the formulation of the finished product.

The composition of the finished product, including quality standard, function, concentration and amount per dose are given in Table 2.

**Table 2** ***Composition of BNT162b2 Tris/Sucrose Finished Product, Multi-dose Vial (225 µg/vial)***

| Name of Ingredients | Reference to Standard | Function | Concentration (mg/mL) | Amount per 0.3 mL dose |
|---|---|---|---|---|
| BNT162b2 drug substance | In-house specification | Active ingredient | 0.1 | 30 µg |
| ALC-0315 | In-house specification | Functional lipid | 1.43 | 0.43 mg |
| ALC-0159 | In-house specification | Functional lipid | 0.18 | 0.05 mg |
| DSPC | In-house specification | Structural lipid | 0.31 | 0.09 mg |
| Cholesterol | Ph. Eur. | Structural lipid | 0.62 | 0.19 mg |
| Sucrose | USP-NF, Ph. Eur. | Cryoprotectant | 103 | 31 mg[b] |
| Tromethamine (Tris base) | USP-NF, Ph. Eur. | Buffer component | 0.20 | 0.06 |
| Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl) | In-house specification | Buffer component | 1.32 | 0.4 |
| Water for Injection | USP-NF, Ph. Eur. | Solvent/vehicle | q.s. | q.s. |

All excipients except the functional lipids ALC-0315 and ALC-0159, the structural lipid DSPC and the buffer component TRIS HCl comply to Ph. Eur. grade. The functional lipids ALC-0315 and ALC-0159 and the structural lipids DSPC and cholesterol are all used in the currently approved PBS/Sucrose finished product Comirnaty. The buffer components Tris base and Tris HCl are commonly used excipients in several already approved parenteral medicinal products.

ALC-0315 and ALC-0159 are novel excipients. In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, additional information was requested as specific obligations (SO) for the PBS/Sucrose finished product. These SOs are included in the ongoing variation EMEA/H/C/005735/II/0054/G. It is confirmed that changes to the lipids also will be implemented for the Tris/Sucrose formulation.

The container closure system for the commercial BNT162b2 Tris/Sucrose finished product is a 2 mL Type I borosilicate or aluminosilicate glass vial and a 13 mm bromobutyl stopper.

The processing aids used in the manufacture have been specified in the composition together with a foot note that they are essentially removed through the manufacturing process and are not considered as ingredients (excipients).

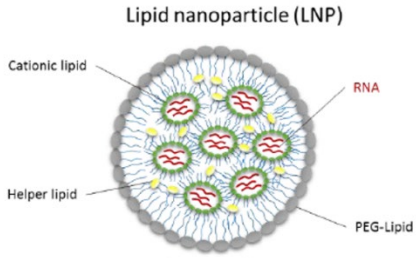
This is found acceptable.

**Pharmaceutical development**

The currently approved PBS/Sucrose finished product Comirnaty, is supplied as a preservative-free, sterile, multidose concentrate of RNA-containing lipid nanoparticles formulated in phosphate buffered saline and sucrose, to be diluted for intramuscular administration. The finished product is diluted with 1.8 mL sterile 0.9% sodium chloride solution to provide 6 doses, each containing a 30 µg active dose in a 0.3 mL dose volume.

The formed RNA-containing LNPs are solid particles relatively homogeneous in size, largely spherical in shape and having a nearly neutral surface. Furthermore, the accumulated batch-data to date of the currently approved PBS/Sucrose finished product show consistent manufacturing of lipid nanoparticles both with respect to size and polydispersity.

*schematic illustration of an exemplary LNP nanoparticle:*




This line extension introduces a Ready To Use (RTU) formulation, referred to as the Tris/Sucrose finished product, that is a preservative-free, sterile dispersion of LNPs in an aqueous cryoprotectant buffer for intramuscular administration. The Tris/Sucrose finished product is formulated at 0.1 mg/mL mRNA in 10 mM Tris buffer, 300 mM sucrose, at a pH of 7.4. Furthermore, the Tris/Sucrose finished product is administered without dilution.

The four lipid excipients, ALC-0315, ALC-0159, DSPC, cholesterol and the sucrose used in the manufacture of the Tris/Sucrose finished product are the same as those used for the current PBS/Sucrose finished product.

Two new excipients, Tris base and Tris HCl, are used in RTU formulation to achieve the desired product pH.

A Quality Target Product Profile (QTPP) was developed for the Tris/Sucrose finished product as a basis for development based upon the currently approved PBS/Sucrose finished product.

***Formulation development***

The development of the Tris/Sucrose finished product showed quality attributes highly comparable and also within the clinical ranges of the current approved PBS/Sucrose finished product but with an improved stability profile in support of increased storage times at -20 °C and 2-8 °C that would simplify transport and administration.

The proposed Tris/Sucrose formulation is equivalent to the current PBS/Sucrose formulation but with the following differences: formulation buffer system (Tris vs PBS), mRNA concentration (0.1 mg/mL vs 0.5 mg/mL) and with an advantage that the proposed Tris/Sucrose finished product does not require dilution upon administration.

The section on formulation development describes and justifies the chosen Tris/Sucrose formulation and is sufficiently comprehensive.

Results are provided in the section on formulation development on both 0.5 mL/vial (single-dose vial) and 2.25 mL/vial (multidose vial) fill volumes. The data provided for a possible future single-dose presentation with a fill-volume of 0.5 mL/vial are considered as supportive data only since it should be noted that this line extension application only includes the multi-dose presentation and that a future introduction of a single dose presentation needs to be applied for via a variation application.

There are no formula overages in the finished product, only an overfill which has been acceptably justified ensuring that six doses can be withdrawn from the multi-dose vial.

The information given on physicochemical and biological properties is found sufficient.

***Manufacturing process development***

*Comparison of manufacturing process design*

The manufacturing process used to produce the Tris/Sucrose finished product includes the same active substance and has the same initial steps as for the currently approved PBS/Sucrose formulation, including the steps of DS thaw and LNP formation and stabilisation. At the Tangential Flow Filtration (TFF) step, Tris buffer is introduced instead of PBS buffer, and the concentration adjustment and cryoprotectant addition step are modified for the Tris/Sucrose formulation. Subsequent steps of sterile filtration, aseptic filling, capping/crimping, labelling and freezing for storage are essentially the same between the Tris/Sucrose and PBS/Sucrose finished products with minor adjustments to reflect the different filling volume.

*Demonstration of comparability*

A comparability study has been performed for three primary Tris/Sucrose finished product lots for ICH stability testing compared to the currently approved PBS/Sucrose finished product. Comparisons used to evaluate comparability were made using the finished product specification acceptance criteria, to pre-determined comparability acceptance criteria from historical release test data for 94 PBS/Sucrose finished product lots as well as to extended characterization testing including a well-characterized reference lot (EL8983).

Tris/Sucrose finished product release data and the extended characterization testing results demonstrated that the Tris/Sucrose finished product lots are comparable to the registered PBS/Sucrose lots, with only few and minor differences noted that are not expected to impact efficacy and safety. All three Tris/Sucrose finished products lots for stability testing met all of the release specifications for the Tris/Sucrose finished product. These three lots also met the established acceptance criteria for the extended characterization testing.

The design of the comparability study utilized for the ICH stability lots has been repeated for three commercial scale PPQ lots. The release data and the extended characterization testing results demonstrated that the Tris/Sucrose PPQ lots product lots are comparable to the registered PBS/Sucrose lots, with only few and minor differences noted that are not expected to impact efficacy and safety. All three Tris/Sucrose PPQ lots met all of the release specifications for the Tris/Sucrose finished product. These three PPQ lots also met the established acceptance criteria for the extended characterization testing.

It is noted that during the PPQ campaign, one PPQ lot () manufactured with split fill with lower fill volumes, had an OOS. This PPQ batch is not included in support of the process validation. Details of the OOS result and an investigation report have been provided in section 3.2.P.3.5. The investigation concluded that no specific

cause could be attributed to the OOS result and two additional PPQ lots were manufactured to complete the validation at 2.25 mL/vial as well as the split fill with lower fill volumes. The conclusions drawn from the investigation report and the actions taken to manufacture a fourth and fifth PPQ batch is supported. This is found acceptable.

In conclusion, the analytical comparability assessment performed demonstrated that the Tris/Sucrose finished product (manufactured at Pfizer, Puurs as primary finished product lots for ICH stability testing (Roll 1 submission) and the three commercial scale PPQ lots (Roll 2 submission)) are comparable to the currently approved PBS/Sucrose finished product.

This is found acceptable.

*Quality attributes*

The quality attributes for the Tris/Sucrose finished product are identical as those for the currently approved PBS/Sucrose finished product.

*Process risk assessment strategy*

The process risk assessment strategy for the Tris/Sucrose finished product is a continuation of the strategy implemented for the currently approved PBS/Sucrose formulation.

*Process development and characterization*

Process development and characterization studies have been sufficiently performed for the unique steps for the Tris/Sucrose formulation.

*Lot genealogy and usage*

Batch data for the three Tris/Sucrose primary stability lots (approximately 7-17% of the planned commercial scale) and the three PPQ lots of finished product are found in section 3.2.P.5.4 and all these lots met all of the release specifications. The batch data also includes both single-dose (1 lot) and multi-dose presentations (2 lots), with the only difference being the fill volume, which is 0.48 mL for single-dose vials and 2.25 mL for the 6 dose multi-dose vials. However, it should be noted that this line extension application only includes the multi-dose presentation and introduction of a single-dose presentation needs to be performed via a variation application.

*Control strategy*

The control strategy for the Tris/Sucrose finished product is based upon and comparable to the control strategy of the currently approved PBS/Sucrose finished product. This is found acceptable.

*Analytical method evolution*

The analytical testing strategy for the Tris/Sucrose finished product assessed each analytical procedure to determine whether changes were required for testing of the Tris/Sucrose finished product.

*Container closure system*

The container closure system for the commercial BNT162b2 Tris/Sucrose finished product is a 2 mL Type I borosilicate or aluminosilicate glass vial and a 13 mm bromobutyl stopper.

*Microbiological attributes and compatibility*

Sufficient information is provided on microbiological attributes.

Results for compatibility support physicochemical stability of the Tris/sucrose finished product in unopened thawed vials for up to 24 hours at 30 °C, and in syringes for up to 24 hours at 2-8 °C and 12 hours at 30 °C. Furthermore, a microbial in-use hold time study was performed by a challenge test including five compendial micro-organisms. No significant growth was observed for any of the microorganisms within 12 hours of inoculation of storage at 20-25 °C.

In conclusion, compatibility of the Tris/sucrose finished product is acceptably demonstrated by the compatibility studies provided on physicochemical stability and microbial in-use hold time.

#### *2.4.3.2. Manufacture of the product and process controls*

The dossier lists the sites that have responsibilities for the production and testing of Tris/Sucrose finished product and their specified functions. All manufacturing sites are already used as manufacturers for the currently approved Comirnaty, concentrate for dispersion for injection (EMEA/H/C/005735, conditional approval 21 Dec 2020). Appropriate proof of GMP compliance of the sites have been provided.

The manufacturing process consists of four major manufacturing steps – LNP fabrication, bulk finished product formation, sterile filtration and aseptic filling.

The manufacturing process for Tris/Sucrose finished product is identical to that for the PBS/Sucrose formulation through LNP formation and stabilization, with subsequent process changes including buffer exchange into Tris buffer instead of PBS, concentration adjustment to 0.1 mg/mL RNA instead of 0.5 mg/mL and fill volume of 2.25 mL instead of 0.45 mL, allowing for administration without dilution.

The Tris/Sucrose finished product is manufactured by Pfizer Puurs. Some supportive data are provided from the manufacturing site Pfizer Kalamazoo which is planned to become a European supply site at a later time point and will by then be submitted as a variation application.

The commercial batch size is 700 – 1600 L of finished product solution corresponding to approximately 311 000 – 711 000 vials at 2.25 mL fill volume.

Sufficient and acceptable in-process controls (IPCs) are applied.

Process validation has been performed on three Process Performance Qualification batches at 1600 L batch scale and of 2.25 mL fill volume. All data complies with the pre-specified criteria and sufficiently demonstrate that the manufacturing process is robust and provide a finished product with adequate quality. The same filling lines and similar hold times and filling times are used for Tris/Sucrose finished product as for the approved PBS/Sucrose finished product and therefore, no new media fill validation has been performed. The applied hold times and the sterilising filters are sufficiently validated. A shipping validation study is performed supporting the transport conditions.

#### *2.4.3.3. Product specification*

The finished product specifications at release and shelf life include tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD), ALC-0159 content (HPLC-CAD), DSPC content (HPLC-CAD), Cholesterol content (HPLC-CAD), vial content (volume) (USP), Lipid identities

(HPLC-CAD), Identity of encoded RNA sequence (RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion). For all quality attributes tested on stability except for RNA integrity and LNP size, the acceptance criteria for release and stability testing throughout shelf life are the same.

*Specification and justification of specifications*

The specifications document for the Tris/Sucrose finished product in section 3.2.P.5.1 includes a comprehensive set of relevant tests along with corresponding acceptance criteria. The specifications and justification of specifications for the Tris/Sucrose finished product are based on the specifications established for the currently approved PBS/Sucrose finished product. The acceptance criteria that differ between the Tris/Sucrose finished product and the currently approved PBS/Sucrose finished product include osmolality, RNA content, lipid content and vial content:

Osmolality: the osmolality is adjusted to reflect the change in buffer system from PBS- to Tris-buffer.

RNA content and lipids content: they are adjusted to the 5-fold difference in concentration and consequential difference in RNA content and lipids content.

Vial content: the acceptance criterion is set to ensure that each vial can deliver six doses and it is approximately 5-fold higher for the Tris/Sucrose finished product compared to the PBS/Sucrose finished product.

Since the acceptance criteria for the Tris/Sucrose finished product are based on the currently approved PBS/Sucrose finished product for the majority of the test attributes, the acceptance criteria for test attributes are considered as clinically qualified to ensure quality, efficacy and safety.

In conclusion, the proposed acceptance criteria in the specifications document in section 3.2.P.5.1 are found acceptable and adequately justified for all quality attributes included and no issues are raised.

*Analytical procedures*

Several of the analytical procedures are identical to the corresponding procedures for the already approved PBS/Sucrose finished product, while others have been updated for analysis of the Tris/Sucrose presentation. Updates include minor modifications in sample preparation and in some cases sample volumes to account for the difference in mRNA concentration between the PBS/Sucrose and Tris/Sucrose presentations. The updated analytical procedures are deemed validated for testing the Tris/Sucrose finished product.

*Batch analyses*

Batch analysis data have been provided for the three Tris/Sucrose primary finished product lots for ICH stability testing as well as for three PPQ batches, all these lots have been manufactured with the commercial manufacturing process at the commercial site Pfizer, Puurs. The manufacture of these lots has been detailed and their genealogies are provided in Section 3.2.P.2.3. All three Tris/Sucrose finished products lots and all three PPQ lots met all of the release specifications for the Tris/Sucrose finished product. Furthermore, the analytical comparability assessment demonstrated that the Tris/Sucrose finished product lots are comparable to the currently approved PBS/Sucrose finished product with only few and minor differences noted that are not expected to impact efficacy and safety. In addition, stability data for the three Tris/Sucrose primary finished product lots for ICH stability testing are provided in section 3.2.P.8.

*Characterization of impurities*

The impurity profile is primarily based on the impurity profile of the materials that are used for the manufacturing as well as the lipid impurities.

The risk assessment for the presence of nitrosamine initially performed for the PBS/Sucrose finished product has been updated for the Tris/Sucrose finished product. The conclusion is that there is no risk of the Tris/Sucrose vaccine containing nitrosamine impurities of concern.

A summary of risk assessment on elemental impurities in line with the ICH Q3D, including analytical data, has been provided. The conclusion is that there is no risk of the Tris/Sucrose vaccine with respect to elemental impurities.

*Reference standard*

The active substance reference material detailed in Section 3.2.S.5.1 Reference Standards or Materials for the currently approved PBS/Sucrose finished product is also used for the Tris/Sucrose finished product for release and stability testing with the Fluorescence assay.

Reference material for the lipids (ALC-0315, ALC-0159, DSPC and cholesterol) is identical to the approved PBS/Sucrose finished product.

The information provided in section P.6 Reference standards or materials is found acceptable.

*Container closure system*

Tris/Sucrose finished product is filled in a Type I borosilicate glass vial or an aluminosilicate glass vial. Both these vials are new for use with Tris/Sucrose finished product, but the same stoppers and seals/caps are used as for the PBS/Sucrose finished product.

### *2.4.3.4. Stability of the product*

The proposed initial shelf-life for the Tris/Sucrose finished product is 6 months when stored at the recommended long-term storage condition of -90 to -60 °C.

The applicant has provided stability results for up to 3 months for three primary stability lots of the Tris/Sucrose finished product as well as initial stability results (release) for the three PPQ lots stored at long term storage condition at -90 to -60 °C. Furthermore, up to 3 months data are provided for the primary stability lots and 1 month data for the PPQ lots at accelerated/additional (-50 ± 5 °C, -20 ± 5 °C, 5 ± 3 °C) and stressed storage conditions as well as for temperature cycling and photostability studies.

The three primary stability lots of the Tris/Sucrose finished product have been manufactured with the commercial manufacturing process at the commercial site and with approximately 7-17% of the planned commercial scale. It is agreed that these batches can be considered as representative of the proposed commercial process for the Tris/Sucrose finished product.

The stability studies are performed in accordance with ICH Q5C (Quality of biotechnological product: Stability testing of biotechnological/biological products) using stability-indicating analytical methods and the same or representative container-closure system as will be used for commercial lots are used in these stability studies.

All stability results for the three primary stability lots stored at -90 to -60 °C and at -20 ± 5 °C complies with the stability acceptance criteria in the finished product specifications document in section 3.2.P.5.1. Overall,

the provided 3 months stability results for the three primary stability lots indicate no signs of degradation, significant trends or changes in terms of quality.

For storage at accelerated/additional storage conditions (-50 ± 5 °C, -20 ± 5 °C, 5 ± 3 °C), the 1 to 3 months stability data met all acceptance criteria.

With regards to photostability, based on the stability results, the SmPC section 6.4 reads "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." and section 6.3 states "Thawed vials can be handled in room light conditions."

For storage at stressed conditions, the 1 month stability data were out of specifications for some quality attributes such as in vitro expression and RNA integrity. These data indicate that the Tris/Sucrose finished product has limited stability at these temperatures studied. This finding is also seen for the currently approved PBS/Sucrose finished product.

Section 6.3 in the SmPC states the following: "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." This statement is supported by the overall picture of the Tris/Sucrose finished product stability based on the provided stability data in section 3.2.P.8 on long-term (at -90 to -60 °C) and additional storage conditions (at -20 ± 5 °C and 2 to 8 °C), the temperature cycling studies as well as the transport validation data provided in section 3.2.P.3.5.

*Post-approval stability protocol and stability commitment*

A minimum of one lot of the Tris/Sucrose finished product will be added at long-term storage condition of -90 to -60 °C to the on-going post-approval stability program annually. The applicant has confirmed that they will continue all the ongoing stability studies at long-term conditions until completion. In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported.

*Concluding remarks on the proposed shelf-life and storage conditions*

The proposed initial shelf-life for the Tris/Sucrose finished product is 6 months when stored at the recommended long-term storage condition of -90 to -60 °C.

The initial shelf life is based primarily on the established stability for the PBS/Sucrose finished product and 3 months of data for the Tris/Sucrose primary stability finished product lots. Additionally, the stability data generated to date on the BNT Tris/Sucrose primary stability lots also support short term storage at 5 ± 3°C for up to 3 months (within the 6 month shelf life). As discussed, and concluded in sections 3.2.P.2.3 and 3.2.P.5.4, it is agreed that the analytical comparability assessment performed has demonstrated that the three Tris/Sucrose finished product lots manufactured at Pfizer, Puurs as primary finished product lots for ICH stability testing (Roll 1 submission) and the three full commercial scale PPQ lots (Roll 2 submission) are comparable to the currently approved PBS/Sucrose finished product.

Therefore, it is agreed that the provided results for Tris/Sucrose formulation combined with the prior knowledge on stability of the PBS/Sucrose formulation support the proposed 6 months shelf-life at -90 to -60 °C and 10 weeks storage at 2-8 °C at the point of use within the 6 months shelf-life, as stated and proposed in section 6.3 in the SmPC.

In addition, the following statement in section 6.3 is also supported by the submitted stability data: "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."

#### *2.4.3.5. Comparability exercise for finished product*

As discussed above.

#### *2.4.3.6. Adventitious agents*

The active substance used to manufacture the Tris/Sucrose finished product is identical to that used for the currently approved PBS/Sucrose finished product. Consequently, there are no changes to the active substance sections and full reference is made to the active substance data of Comirnaty, concentrate for dispersion for injection, (EMEA/H/C/005735). Adequate testing for bioburden, endotoxins and sterility are also included at appropriate stages of the manufacturing process of the finished product.

#### *2.4.3.7. GMO*

Not applicable.

### 2.4.1. Finished Medicinal Product – (0.5 mg/ml) concentrate for dispersion for injection

The following changes are proposed to the product information of the currently authorised Comirnaty concentrate for dispersion for injection;

- Type IB C.I.z - To update sections 6.4, 6.5 and 6.6 of the SmPC, section 5, 6 and information for healthcare professionals of the PL, section 1 of the Carton Box Label as well as section 1 and 5 of the Vial Label to ensure the correct handling by providing dose verification information about strength, age range, colour information of the flip-off plastic cap and greyscale images.
- Type IB C.I.z - To update sections 4.2 of the SmPC ensure the correct handling in accordance to interchangeability of the medicinal product.
- Type IB C.I.z - To update section 8 of Carton Box Label to clarify expiry date "EXP" by adding storage temperature "(at -90°C to -60°C)" to ensure the correct handling of the medicinal product.
- Type IA A.3 - To change the name of the active substance from COVID-19 mRNA Vaccine (nucleoside modified) to Tozinameran.

The proposed changes to product information (SmPC, Labelling and Package Leaflet) are found acceptable.

### 2.4.2. Discussion on chemical, pharmaceutical and biological aspects

This line extension introduces a Ready To Use (RTU) formulation, referred to as the Tris/Sucrose finished product, that is a preservative-free, sterile dispersion of LNPs in an aqueous cryoprotectant buffer for intramuscular administration. The Tris/Sucrose finished product is formulated at 0.1 mg/mL mRNA in 10 mM Tris buffer, 300 mM sucrose, at a pH of 7.4. Furthermore, the Tris/Sucrose finished product has been developed to provide a vaccine with an improved stability profile and greater ease of use at administration sites.

The section on formulation development describes and justifies the chosen Tris/Sucrose formulation and is sufficiently comprehensive.

The analytical comparability assessment performed demonstrated that lots manufactured as primary finished product lots for stability testing and the commercial scale PPQ lots of the Tris/Sucrose finished product are comparable to the currently approved PBS/Sucrose finished product.

The manufacturing process for Tris/Sucrose finished product is identical to that for the PBS/Sucrose formulation through LNP formation and stabilization, with subsequent process changes including buffer exchange, concentration adjustment, and fill volume. The manufacturing process has been acceptably described.

The specifications document for the Tris/Sucrose finished product includes a comprehensive set of relevant tests and the proposed acceptance criteria are found acceptable and adequately justified for all quality attributes included and no issues are raised.

The proposed 6 months shelf-life for the finished product at -90 to -60 °C and 10 weeks storage at 2-8 °C at the point of use within the 6 months shelf-life is agreed.

The proposed changes to product information (SmPC, Labelling and Package Leaflet) of the currently approved Comirnaty concentrate formulation are found acceptable.

### 2.4.3. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided in rolling review 2 (RR2) submission, the CHMP considers that this line extension application to register Comirnaty 0.1 mg/ml (30 micrograms/dose) dispersion for injection is approvable from the quality point of view.

Furthermore, the grouped Type IB variations included in the submission to amend the current SmPC, label and package leaflet of the approved Comirnaty 0.5 mg/ml (30 micrograms/dose) concentrate formulation and the Type IA variation to change the active substance name from 'COVID-19 mRNA Vaccine (nucleoside modified)' to the INN 'Tozinameran' are approvable from the quality point of view.

### 2.4.4. Recommendations for future quality development

Not applicable.

## *2.5. Non-clinical aspects*

Not applicable, reference is made to the data of Comirnaty, concentrate for dispersion for injection, (EMEA/H/C/005735).

## *2.6. Clinical aspects*

Not applicable, reference is made to the data of Comirnaty, concentrate for dispersion for injection, (EMEA/H/C/005735).

## *2.7. Risk Management Plan*

### 2.7.1. Safety concerns

No change in this section in the RMP submitted with this application.

### 2.7.2. Pharmacovigilance plan

The MAH has included a discussion on the potential for medication errors with the new formulation. In response to the two outstanding issues, the MAH confirmed that the existing and the new formulation would co-exist on the EU market until the end of 2022, and that adequate measures have been put in place to monitor and report any emerging trend in the pattern of reporting that might be related to the new formulation.

No change in the additional pharmacovigilance activities proposed in the RMP submitted with this application.

### 2.7.3. Risk minimisation measures

No change in this section in the RMP submitted with this application.

### 2.7.4. Conclusion

The CHMP considered that the risk management plan version 2.4 is acceptable.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

## *2.9. Product information*

### 2.9.1. User consultation

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Comirnaty concentrate for dispersion for injection,

EMEA/H/C/005735/0000/RR.

The bridging report submitted by the applicant has been found acceptable.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS) (for further descriptions see also previous assessments for Comirnaty, CMA, and subsequent variations).

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.

### 3.1.2. Available therapies and unmet medical need

There are currently four approved vaccines in the EU available to prevent COVID-19. Several development programs are ongoing globally and currently other applications are under evaluation by regulatory authorities worldwide. There is a very high global demand for vaccines to help contain the pandemic and decrease morbidity and mortality in at risk groups.

### 3.1.3. Main clinical studies

No clinical studies were included in this application.

## *3.2. Favourable effects*

No new clinical data are included in this application.

## *3.3. Uncertainties and limitations about favourable effects*

No new clinical data are included in this application.

## *3.4. Unfavourable effects*

No new clinical data are included in this application.

## 3.5. Uncertainties and limitations about unfavourable effects

No new clinical data are included in this application.

## 3.6. Benefit-risk assessment and discussion

No new clinical data are included in this line extension application. The available data are supportive of a positive B/R balance for the proposed indication.

***Conditional marketing authorisation***

This is a line extension application, new strength and new pharmaceutical form, to Comirnaty, concentrate for dispersion for injection (EMEA/H/C/005735) which received a conditional approval 21 December 2020.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the prevention of a life-threatening disease, is to be used in emergency situations in response to public health threats duly recognised by the World Health Organisation and EU.

The product is considered to fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.
- An unmet medical needs will be addressed in a situation of a global pandemic.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

## 3.7. Conclusions

The overall benefit/risk balance of COMIRNATY dispersion for injection, is positive, subject to the conditions stated in section 'Recommendations'.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, the CHMP considers by consensus that the benefit-risk balance of, COMIRNATY 30 micrograms/dose (0.1 mg/ml) dispersion for injection is favourable in the following indication:

> *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.*

The CHMP therefore recommends the extension of the marketing authorisation for COMIRNATY subject to the following conditions and specific obligations:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to medical prescription.

***Official batch release***

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

***Conditions and requirements of the marketing authorisation***

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports 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.

***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.

***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, as agreed at the time of initial cMA:

| 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 |

| Description | Due date |
|---|---|
| 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 |
| 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 |

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

| Variations requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | IB | I |
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | IB | IIIA |
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | IB | I, IIIA and IIIB |
| A.3 | A.3 - Administrative change - Change in name of the AS or of an excipient | IAin | I, IIIA and IIIB |

- Update sections 6.4, 6.5 and 6.6 of the SmPC, section 5, 6 and information for healthcare professionals of the PL, section 1 of the Carton Box Label as well as section 1 and 5 of the Vial Label to ensure the correct handling by providing dose verification information about strength, age range, colour information of the flip-off plastic cap and greyscale images.
- Update sections 4.2 of the SmPC ensure the correct handling in accordance to interchangeability of the medicinal product.
- Update section 8 of Carton Box Label to clarify expiry date "EXP" by adding storage temperature "(at -90°C to -60°C)" to ensure the correct handling of the medicinal product.
- Change the name of the active substance from COVID-19 mRNA Vaccine (nucleoside modified) to Tozinameran.

The marketing authorisation holder has taken the opportunity to implement minor editorial changes.