



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

22 June 2023  
EMA/355551/2023  
Committee for Medicinal Products for Human Use (CHMP)

## CHMP assessment report on extension of marketing authorisation

COMIRNATY

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/X/0180

### Note

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



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# 1. Background information on the procedure

## 1.1. Submission of the dossier

BioNTech Manufacturing GmbH submitted on 19 April 2023 an extension of the marketing authorisation.

Extension application to add a new pharmaceutical form of Comirnaty 5/5 µg (tozinameran, famtozinameran) dispersion for injection for children aged 5 to 11 years of age.

The MAH applied for an addition of a new pharmaceutical form dispersion for injection.

The MAH applied for the following indication for Comirnaty 5/5 micrograms/dose:

*Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.*

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

## 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, (2) point (d) - Extensions of marketing authorisations.

## 1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0466/2022 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0466/2022 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 did not seek Scientific advice at the CHMP.

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

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

The application was received by the EMA on	19 April 2023
The procedure started on	22 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 June 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 June 2023
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	22 June 2023

## **2. Scientific discussion**

### **2.1. Problem statement**

#### **2.1.1. Disease or condition**

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission.

#### **2.1.2. Clinical presentation**

COVID-19 presentation is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic patients, disease progression may lead to acute respiratory distress syndrome requiring ventilation, subsequent multi-organ failure, and death.

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

### **2.1.3. Management**

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, vaccination is the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus.

## **2.2. About the product**

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection is authorized with the indication for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years who have previously received at least a primary vaccination course against COVID-19. This application concerns a new pharmaceutical form (dispersion for injection) for Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose multidose and single dose vials.

## **2.3. General comments on compliance with GMP, GLP, GCP**

The review of the manufacturer information in Module 1 is within the remit of the EMA Inspections Office. The EMA Compliance and Inspection Service has reviewed the manufacturer information contained in the application form and available certificates from the EEA National Competent Authorities and they are found acceptable.

## **2.4. Quality aspects**

### **2.4.1. Introduction**

Pfizer and BioNTech have developed the COMIRNATY vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus SARS-CoV-2. The vaccine is based on SARS CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs).

There are several approved formulations of Comirnaty vaccine:

- PBS/Sucrose finished product, *Comirnaty, 30 micrograms/dose, concentrate for dispersion for injection* which received a conditional approval 21 December 2020 (EMA/H/C/005735)
- Tris/Sucrose finished product, *Comirnaty, 30 micrograms/dose, dispersion for injection*, approved 3 November 2021 (EMA/H/C/005735/X/0044)
- Tris/Sucrose finished product, *Comirnaty, 10 micrograms/dose, concentrate for dispersion for injection*, approved 26 November 2021 (EMA/H/C/005735/X/0077)

- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.1, (15/15 micrograms)/dose, dispersion for injection*, approved 1 September 2022 (EMA/H/C/005735/II/0140)
- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.4-5, (15/15 micrograms)/dose, dispersion for injection*, approved 12 September 2022 (EMA/H/C/005735/II/0143)
- Tris/Sucrose finished product, *Comirnaty, 3 micrograms/dose, concentrate for dispersion for injection*, approved 20 October 2022 (EMA/H/C/005735/X/0138)
- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.4-5, (5/5 micrograms)/dose, concentrate for dispersion for injection*, approved 10 November 2022 (EMA/H/C/005735/X/0147)
- Tris/Sucrose finished product, *Comirnaty Original/Omicron BA.4-5, (1.5/1.5 micrograms)/dose, concentrate for dispersion for injection*, under review, outcome June 2023 (EMA/H/C/005735/X/176)

This line extension introduces 0.033 mg/mL finished product presentations which do not require dilution. A finished product presentation which does not require dilution offers improved ease of use and enables presentation as a single-dose vial. For these reasons, 0.033 mg/mL in Tris buffer, sucrose, presentations were developed to provide 10 µg doses presented in a single- or multi-dose vial. The proposed finished product presentation is a preservative-free, sterile dispersion of lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for intramuscular administration.

For a multi-dose vial presentation, the finished product is filled at 2.25 mL per vial and is administered without dilution providing 6 doses of 10 µg RNA each in a 0.3 mL injection volume. The single-dose vial presentation is filled at 0.48 mL fill volume per vial and is administered without dilution providing 1 dose of 10 µg RNA in a 0.3 mL injection volume.

The Tris/Sucrose vaccine presentations of 0.033 mg/mL are being introduced based on the vaccine platform established for the 0.1 mg/mL vaccine. The overall manufacturing process and equipment remain unchanged. Process validation has been completed with three Process Performance Qualification (PPQ) lots. An acceptable bracketing approach is used to cover both single-dose vials (SDV) and multi-dose vials (MDV). There are no changes to finished product specifications with the exception of related to the lower concentration of the presentation. Stability studies are ongoing.

## **2.4.2. Active Substance**

The active substances tozinameran and famtozinameran are already approved for the original Comirnaty vaccine formulations (EU/1/20/1528/001-014). No changes to the information are proposed for the active substance.

## **2.4.3. Finished Medicinal Product**

### **2.4.3.1. Description of the product and Pharmaceutical Development**

The BNT162b2 Bivalent [Original and Omicron (BA.4/BA.5) Variant] finished product (herein referred to as Bivalent), is supplied as a preservative-free, sterile dispersion of RNA containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer for intramuscular administration.

There are 5 presentations for the Bivalent finished product providing doses of either 30 or 10 µg of RNA per dose in multi-dose vial (MDV) and single-dose vial (SDV) presentations.

Each presentation is formulated in Tris buffer, sucrose, contains a 1:1 ratio of the Original and Omicron BA.4/BA.5 RNA constructs. As each construct, BNT162b2 Original and Omicron BA.4/BA.5, is present in approximately equal quantities, the 30 µg dose contains 15 µg of each construct, and the 10 µg dose contains 5 µg of each construct. The ratio of RNA to lipid components is also constant across the presentations. The presentations differ in RNA concentration, fill volume, and requirement for dilution prior to administration and are summarized in Table 1.

The composition of the finished product, including quality standard, function, concentration and amount per dose for the 30 µg dose finished product presentations has been provided. The same information for presentations of the 10 µg dose which do not require dilution has been provided.

Section 3.2.P.1 has been appropriately updated to include the 10 µg dose presentation of the bivalent vaccine (10 µg total RNA in a 0.3 mL injection volume), a ready-to-use formulation, which do not require dilution compared to the already approved procedures EMEA/H/C/005735/X/147 (10 µg total RNA/dose, bivalent vaccine, dilution required) as well as EMEA/H/C/005735/X/0077 and EMEA/H/C/005735/II/0143.

This line extension introduces 0.033 mg/mL of total RNA bivalent finished product presentations which do not require dilution. These presentations include bivalent 0.033 mg/mL of total RNA in Tris buffer and sucrose, to provide 10 µg doses in a 0.3 mL injection volume presented in a single- (SDV) or multi-dose vial (MDV). These presentations include an approximate 1:1 ratio of the original and omicron BA.4/BA.5 variant strains. For a multi-dose vial presentation, the finished product is filled at 2.25 mL per vial and is administered without dilution providing 6 doses of 10 µg RNA each in a 0.3 mL injection volume. The single-dose vial presentation is filled at 0.48 mL fill volume per vial and is administered without dilution providing 1 dose of 10 µg RNA in a 0.3 mL injection volume.

The function of each excipient in the formulation remains unchanged from the 0.1 mg/ml presentations. 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, the structural lipid DSPC and the buffer component Tris HCl are all used in the currently approved Tris/sucrose and PBS/sucrose finished products of Comirnaty.

The container closure system is a 2 mL Type I borosilicate or aluminosilicate glass vial and a 13 mm bromobutyl rubber stopper and is the same container closure system as for the already approved Tris/sucrose finished product of Comirnaty.

The processing aids and active substance formulation buffer components are residues that are essentially removed through the manufacturing process and are not considered as ingredients (excipients).

### **Pharmaceutical development**

The pharmaceutical development information has been updated and revised to include the new bivalent 0.033 mg/mL finished product formulation with no dilution required upon administration and to include a description of the manufacturing process and development studies performed for the 0.033 mg/mL finished product.

The development and manufacturing process of the 0.033 mg/mL finished product is at large based on the 0.1 mg/mL finished product, with differences limited to the lower lot size and the lower concentration of the product but also with the exception that the final dilution step adjusts the concentration of the finished

product to 0.033 mg/mL RNA. The ratio of RNA to lipid components remains constant across the 0.1 mg/mL and 0.033 mg/mL presentations.

The release specifications are the same across the 0.033 mg/mL and 0.1 mg/mL, except for changes related to the lower concentration of the 0.033 mg/mL presentation. It is stated by the applicant that development of the 0.1 mg/mL finished products is considered to be supportive of the 0.033 mg/mL finished products as the process used to produce the finished product at 0.033 mg/mL is highly similar to that of the 0.1 mg/mL presentations, and this is agreed to. However, as the lower concentration of the 0.033 mg/mL may impact stability of the finished product, the shelf life of the 0.033 mg/mL finished product is established separately from the 0.1 mg/mL finished product presentations.

A revised QTPP has been provided including the 0.033 mg/mL finished product.

Comparability has previously been acceptably demonstrated between clinical and commercial scale original finished product, between various manufacturing sites, between the PBS/sucrose finished product and Tris/sucrose finished product, between the various dosage presentations (30, 10 and 3 µg) as well as between the monovalent and bivalent vaccine finished product. Comparability has been demonstrated via comprehensive studies including both release testing and extended characterisation testing. Due to the application of the same formulation, very similar manufacturing process and the use of the same manufacturing sites as the already authorized products, extensive prior experience is leveraged for the bivalent 10 µg presentations of finished product at 0.033 mg/mL of total RNA content (no dilution required) to the 0.1 mg/mL finished product presentations and comparability it is therefore considered sufficiently demonstrated by the evaluation of release testing results against the acceptance criteria in the finished product specification.

Information on lot genealogies of three PPQ lots for process validation and three lots for stability testing has been provided. All these lots have been manufactured at Pfizer, Puurs and for the bivalent 10 µg presentations of finished product (0.033 mg/mL of total RNA content, no dilution required).

Furthermore, for the bivalent 10 µg presentations of finished product (0.033 mg/mL of total RNA content no dilution required), batch analysis data are provided for the batches manufactured to date including PPQ-batches and batches for stability testing.

#### *Container closure system*

The container closure system information has been revised and updated to include the 0.033 mg/mL presentation of the vaccine finished product.

Compatibility studies supporting the 0.033 mg/mL presentation of the vaccine finished product have been provided.

Dose verification studies were performed to demonstrate that the 10 µg RNA dosing solution at 0.033 mg/mL RNA concentration is compatible with commonly available administration components for intramuscular injection and that dosing solutions are stable in the administration components for a period of time adequate to perform the dose preparation and administration operations.

Results of the compatibility study have been provided for three finished product and there was no change in any of the tested attributes for the finished product in vials or syringes. All results remain within the pre-determined acceptance criteria.

In conclusion, the information provided on Pharmaceutical development is found sufficient and acceptable.

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

The bivalent BA.4-5 vaccine (5/5 micrograms)/dose, ready-to-use formulation, is manufactured at manufacturing sites, and using the same platform manufacturing process, as currently approved Comirnaty vaccines (Tris/Sucrose formulation) (EU/1/20/1528/002-014). The GMP compliance of these sites has been previously confirmed.

Comirnaty, (5/5 micrograms)/dose, dispersion for injection (no dilution required) is manufactured by Pfizer Manufacturing Belgium NV, Puurs, Belgium . Some quality control tests are also performed by Pfizer Ireland Pharmaceuticals, Dublin, Ireland. Responsible for batch release in EU is Pfizer Manufacturing Belgium NV, Puurs, Belgium and BioNTech Manufacturing GmbH, Mainz, Germany.

The manufacturing process consists of four major manufacturing steps – LNP fabrication, bulk drug product formation, sterile filtration and aseptic filling. The manufacturing process is the same as for the bivalent BA.4-5 vaccine (5/5 micrograms)/dose (EMA/H/C/005735/X/147) except for the buffer exchange and concentration steps. The manufacturing process is sufficiently described, and suitable in-process controls (IPCs) are applied.

Process validation has been performed on three PPQ batches . All data comply with the pre-specified criteria and sufficiently demonstrate that the manufacturing process is robust and provides a drug product with adequate quality.

A simulated shipping validation study has also been performed which support shipments of 0.033 mg/mL drug product in the same manner as the 0.1 mg/mL drug product.

### **2.4.3.3. Product specification, analytical procedures, batch analysis**

The finished product specifications for the bivalent vaccine finished product include tests for 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), RNA ratio (ddPCR), ALC-0315 content (HPLC-CAD, HPLC-ELSD), ALC-0159 content (HPLC-CAD, HPLC-ELSD), DSPC content (HPLC-CAD, HPLC-ELSD), Cholesterol content (HPLC-CAD, HPLC-ELSD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD, HPLC-ELSD), Identity of encoded RNA sequence (ddPCR), 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).

The specifications for the bivalent 10 µg/dose, 0.033 mg/mL vaccine finished product (ready-to-use solution, no dilution required) includes a comprehensive set of relevant tests along with corresponding acceptance criteria and are based on those established for the already approved bivalent 10 µg/dose, 0.1 mg/mL vaccine finished product. The acceptance criteria for release and stability testing for the bivalent 10 µg/dose, 0.033 mg/mL vaccine finished product are the same as for the bivalent 10 µg/dose, 0.1 mg/mL vaccine finished product for all quality attributes tested except for RNA content and lipid content that are related to the lower concentration, i.e. total RNA content of 0.033 mg/mL vs 0.1 mg/mL.

The specification has been updated with new acceptance criteria for the following parameters: RNA content and lipids content.

The provided justifications for RNA content and lipid content are found acceptable.

Furthermore, since the acceptance criteria for the bivalent 10 µg/dose, 0.1 mg/mL vaccine finished product are based on those established for the already approved bivalent 10 µg/dose, 0.1 mg/mL vaccine finished product for the majority of test attributes, these acceptance criteria for test attributes are considered as clinically qualified to ensure quality, efficacy and safety.

The analytical procedures have been described in sufficient detail and have been validated in line with ICH Q2 guideline. Relevant supplemental validation data, i.e. additional qualification for a subset of assay characteristics due to the decrease in RNA concentration, has been provided.

Batch analysis data has been provided for three full commercial scale PPQ batches manufactured for process validation) and three primary stability batches for stability testing,(clinical lots)). All batches were manufactured at Pfizer, Puurs. All results met the acceptance criteria at the time of release. Stability studies are ongoing on all three PPQ batches as well as for the primary stability batches.

#### **2.4.3.4. Stability of the product**

Stability data are provided from three primary stability lots stored up to 12-months at long-term storage conditions (-90 to -60 °C) and 6-months at accelerated storage conditions (5 ± 3 °C). Additional stability data are provided for three PPQ batches stored up to 6-months at long-term storage conditions (-90 to -60 °C) and 3-months at accelerated storage conditions (5 ± 3 °C).

All stability results available for the primary stability batches and the PPQ batches stored at the recommended long-term storage condition of -90 to -60 °C comply with the proposed end-of-shelf life/stability specification for the bivalent 10 µg/dose, 0.033 mg/mL, vaccine finished product.

Furthermore, it can be noted, that extensive prior experience is leveraged for the bivalent 10 µg presentations of finished product at 0.033 mg/mL of total RNA content (ready-to-use presentation, no dilution required) to the bivalent 0.1 mg/mL finished product presentations (dilution required) and comparability has been sufficiently demonstrated between both these two bivalent 10 µg presentations.

The proposed shelf-life for the bivalent 10 µg/dose, 0.033 mg/mL vaccine finished product (ready-to-use, no dilution required) of 12 months when stored at the recommended long-term storage condition of -90 to -60 °C including a short-term storage at 5±3 °C for up to 10 weeks (within the 12 months shelf-life), as defined in SmPC Section 6.3, is acceptable.

#### **2.4.3.5. Post approval change management protocol(s)**

Not applicable.

#### **2.4.3.6. Adventitious agents**

The active substances (tozinameran and famtozinameran) are identical to that used for the currently approved Comirnaty vaccine formulations (EU/1/20/1528/001-014). 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 (EMA/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.

#### **2.4.4. Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

#### **2.4.5. Conclusions on chemical, pharmaceutical and biological aspects**

This line extension application to register Comirnaty Original/Omicron BA.4-5, (5/5 micrograms)/dose, dispersion for injection, is recommended for approval from a quality point of view.

#### **2.4.6. Recommendation(s) for future quality development**

Not applicable.

### **2.5. Non-clinical aspects**

This application concerns new pharmaceutical form (dispersion for injection) for Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose multidose and single dose vials. No non-clinical data has been provided.

### **2.6. Clinical aspects**

This application concerns new pharmaceutical form (dispersion for injection) for Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose multidose and single dose vials. No clinical data has been provided.

### **2.7. Risk Management Plan**

#### **2.7.1. Safety concerns**

No changes regarding safety specification are proposed in RMP v 9.2.

#### **2.7.2. Pharmacovigilance plan**

##### **Routine pharmacovigilance**

Section III.1 Routine pharmacovigilance was largely unchanged relative to the approved RMP version 9.0, with the exception of the following amendments (added text in blue, deleted text in strike-through):

- **Potential Medication Errors**

This section is applicable to all formulations presented in the RMP.

Large scale public health approaches for mass vaccination may represent changes to standard ~~vaccine treatment processes~~ vaccination processes, thereby potentially ~~increasing~~ introducing the risk of medication errors related to: ~~reconstitution-dilution~~ and administration, vaccination scheme, storage conditions, ~~errors associated with use of~~ a multi-dose vial, ~~availability of~~ different formulations and multiple presentations, and confusion with other COVID vaccines. These potential medication errors are mitigated through the information in the SmPC and available resources and referenced materials for healthcare providers and individuals receiving vaccination:

- The EU-SmPC (section 6.6) contains instructions for ~~vaccine reconstitution~~ dilution and administration, vaccination ~~scheme-dosing~~, and storage conditions ~~for~~ of the formulations of the COVID-19 mRNA vaccine.
- Reference A-posters with step-by-step instruction for vaccine storage, vial differentiation, dose planning and preparation, and administration ~~is~~ are available, ~~which and~~ can be conspicuously displayed in vaccination settings ~~where vaccine is to be administered~~ for ongoing reference.
- Reference brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- ~~A-Dosing card~~ Dosing card which provides information for vaccine storage, vial differentiation, dose planning, and administration is available, ~~which is available~~ for healthcare provider reference.
- Medical information call centers ~~will be~~ are available for healthcare providers to obtain information on use of the vaccine.
- Patient Traceability and Vaccination Reminder card (Annex 7) will be provided with the pre-printed manufacturer name, placeholder spaces for dates of vaccinations and batch/lot numbers as a mitigation effort for potential confusion between vaccines (see Traceability for additional details).

These available resources will inform healthcare providers on the proper preparation and administration of various formulations of the vaccine and reduce the potential for medication error in the context of a mass vaccination campaign. ~~In addition, HCP's will receive communication to inform of availability of these resources and/or new vaccine presentations, when applicable.~~ Additionally, the patient information leaflet and Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

#### *Vial Differentiation*

All vials have specific colour flip off plastic cap and label differentiation factors:

In Tables 71-73 Vaccine Presentation Characteristics [not reproduced here] the new formulation has been added.

Large scale public health approaches for vaccination may represent changes to standard vaccine treatment process with the use of various formulations to different healthcare settings based on age (ie. less than 12 years and above 12 years of age). This represents the likelihood of the ~~purple and grey~~ different colours vials

co-existing in the same setting. These potential medication errors are mitigated through the information in the label (colour of label boarder, product name on the label) and available resources and referenced materials for healthcare providers.

#### PBS-Sucrose formulation

**Comirnaty 30 mcg/ dose - 12 years of age and older, Dilute before use - Purple cap:** If 1.8 mL sodium chloride solution is not added to the 30 mcg/dose concentrate for dispersion for injection vial (purple cap), the user would only be able to extract approximately 1 dose instead of 6 doses as the filled volume is 0.45 mL.

#### Tris-Sucrose formulation

This drug product formulation is referred to as the 'Tris-Sucrose formulation' to emphasize the change in formulation buffer.

**Comirnaty 30 mcg/dose - 12 years of age and older, Do not dilute - Grey cap:** If an attempted is made to further dilute the 30 mcg/dose dispersion for injection vial (~~grey cap~~), the a user would immediately experience feel resistance to the addition of any further volume because as the vial filled volume is 2.25 mL and therefore there is little remaining physical space to add additional diluent to the vial.

**Comirnaty Original/Omicron BA.1 (15/15 mcg)/dose - 12 years of age and older, Do not dilute - Grey cap:** If an attempted is made to further dilute the 30 mcg/dose dispersion for injection vial (~~grey cap~~), the a user would immediately experience feel resistance to the addition of any further volume as because the vial filled volume is 2.25 mL and therefore there is little remaining physical space to add additional diluent to the vial.

**Comirnaty Original/Omicron BA.4-5 (15/15 mcg)/dose - 12 years of age and older, Do not dilute - Grey cap:** If an attempted is made to further dilute the 30 mcg/dose dispersion for injection vial (~~grey cap~~), a the user would immediately experience feel resistance to the addition of any further volume as because the vial fill volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial.

**Comirnaty Original/Omicron BA.4-5 (15/15 mcg)/dose - 12 years of age and older, Do not dilute - Light Grey cap:** The fill volume for this light grey cap vial is only 0.48 mL because it contains 1 dose for extraction. If diluted with sodium chloride 9 mg/mL (0.9%) solution by mistake, more than 1 dose of over diluted vaccine may be erroneously extracted.

**Comirnaty 10 mcg/dose - 5 through 11 years of age, Dilute before use - Orange cap:** If the contents of the vial are attempted to not diluted with the required 1.3 mL sodium chloride 9 mg/mL (0.9%) solution, the user would only be able to extract approximately 5 doses instead of 10 doses as because the filled volume is 1.3 mL. If excess diluent such as 1.8 mL of diluent, which is the dilution volume for the 30 mcg/dose diluted product (purple cap amount), is used to dilute the 10 mcg/dose vial, it would be difficult to add the entire volume of diluent into the vial, and the preparer will likely feel resistance.

**Comirnaty Original/Omicron BA.4-5 (5/5 mcg)/dose - 5 through 11 years of age, Dilute before use - Orange cap:** If the contents of the vial are attempted to not diluted with the required 1.3 mL sodium chloride 9 mg/mL (0.9%) solution, the user would only be able to extract approximately 5 doses instead of 10 doses as because the filled volume is 1.3 mL. If excess diluent such as 2.2 mL of diluent, which is the dilution volume for the 3 mcg/dose diluted product (maroon cap amount), is used to dilute the 10 mcg/dose

vial, it would be difficult to add the entire volume of diluent into the vial, and the preparer will likely feel resistance.

**Comirnaty Original/Omicron BA.4-5 (5/5 mcg)/dose - 5 through 11 years of age, Do not dilute - Dark Blue cap:** If an attempt is made to dilute the 10 mcg/dose dispersion for injection vial (dark blue cap), the user would immediately feel resistance to the addition of any further volume, because the filled volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial.

**Comirnaty Original/Omicron BA.4-5 (5/5 mcg)/dose - 5 through 11 years of age, Do not dilute - Light Blue cap:** The fill volume for the light blue cap presentation is 0.48 mL because it contains 1 dose for extraction. If diluted with sodium chloride 9 mg/mL (0.9%) solution by mistake, the user would be able to extract multiple doses and the product would be over diluted and not achieve the appropriate dose level if administered.

**Comirnaty 3 mcg/dose - 6 months through 4 years of age, Dilute before use - Maroon cap:** If the contents of the vial are attempted to not diluted with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution, the user would only be able to extract approximately 1 dose instead of 10 doses as because the filled volume is 0.4 mL. If 1.8 mL of diluent (purple cap amount) or 1.3 mL of diluent (orange cap amount) were used, this would be an under dilution and would also reduce the number of doses able to be extracted from retrieved-out of the vial, which might indicate to the HCP that there had been an error in preparation.

Various resources and referenced resources to inform HCPs on the proper preparation and differentiation will be available.

### 2.7.3. Risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that: the proposed risk minimisation measures, which have not changed, are sufficient to minimise the risks of the product in the proposed indication(s).

### 2.7.4. Conclusion

After the PRAC meeting, the MAH took the opportunity and submitted RMP version 10.0, merging versions 9.2, 9.3, and 9.4 of the RMP submitted and reviewed with this procedure, procedure X176, and II177, and implementing an agreed 6 months delay for interim report of study C4591007. The CHMP considered that the risk management plan version 10.0 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 information leaflet (PL) has been performed on the basis of a bridging report making reference to Comirnaty concentrate for dispersion for injection, COVID-19 mRNA Vaccine (nucleoside modified); 30 micrograms/dose – adults and adolescents from 12 year, EMEA/H/C/005735/0000, dated: 21 December 2020.

Assessment of the Bridging proposed by the applicant was performed. In the assessment report for Procedure No. EMEA/H/C/005735/X/0176, unfortunately it was referred to the wrong product. Reference was made to Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection, while it should be referred to Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose dispersion for injection. However, the same grounds for bridging have been used in both procedures and bridging is acceptable in both cases.

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

### **2.9.2. Labelling exemptions**

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.1, from 16 December 2020)5 document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities.

- English-only labelling (inner and outer label/carton) and package leaflet\* (from start of supply until end 2023).
- Without country-specific information, such as blue box requirements (from start of supply until end 2023).

All MSs (with one exception: Poland\*\*) have agreed to extend the current derogations until the end of 2023; this will allow the MAH to make all necessary adjustments so that by Jan 2024 the MAH can revert to full EU labelling requirements.

\*MAH should ensure provision of the package leaflet in national language(s) to relevant member states, separately to vaccine supply, as stated in Q2 Q&A flexibilities for COVID-19 vaccines with the exception of Germany.

\*\*The MAH should address this labelling exemption request directly to the Polish NCA.

### **2.9.3. Quick Response (QR) code**

The updates of the QR code/URL to include further references to Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection, as well as the necessary layout changes on the website shall be submitted and assessed via an Article 61.3 notification (post-authorisation).

### **2.9.4. Additional monitoring**

Pursuant to Article 23(1) of Regulation No (EU) 726/2004 (REG), Comirnaty (tozinameran) is included in the additional monitoring list as a new active substance and new biological.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

## **3. Benefit-Risk Balance**

### **3.1. Introduction**

This application concerns new pharmaceutical form (dispersion for injection) for Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose multidose and single dose vials.

In accordance with the recommendations from the EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants ([https://www.ema.europa.eu/en/documents/other/ecdc-ema-statement-updating-covid-19-vaccines-composition-new-sars-cov-2-virus-variants\\_en.pdf](https://www.ema.europa.eu/en/documents/other/ecdc-ema-statement-updating-covid-19-vaccines-composition-new-sars-cov-2-virus-variants_en.pdf)), the vaccine posology has been simplified for all approved formulations.

### **3.2. Therapeutic Context**

#### **3.2.1. Disease or condition**

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human-to-human transmission.

#### **3.2.2. Available therapies and unmet medical need**

Currently available therapies have different benefit-risk considerations depending on the stage of illness and disease manifestations. While care for individuals who have COVID-19 has improved with clinical experience, vaccination has been the most effective medical countermeasure to decrease risk and mitigate spread of the SARS-CoV-2 virus.

### **3.2.3. Main clinical studies**

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection is authorized with the indication for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years who have previously received at least a primary vaccination course against COVID-19. This application concerns a new pharmaceutical form (dispersion for injection) for Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose multidose and single dose vials. No clinical studies have been performed.

### **3.3. Benefit-risk assessment and discussion**

#### **3.3.1. Balance of benefits and risks**

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection is authorized with the indication for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years. No new clinical data has been presented in this application since it concerns a new pharmaceutical form only. The benefit risk balance has not changed and remains positive.

### **3.4. Conclusions**

The overall benefit /risk balance of Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection multidose and single dose vials is positive.

## **4. Recommendations**

### **Outcome**

Based on the CHMP review of data on quality and safety, the CHMP considers by consensus that the benefit-risk balance of Comirnaty BA.4-5 (5/5 micrograms)/dose dispersion for injection (multidose and single dose vials) is favourable in the following indication:

*Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.*

*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:

### **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.

## ***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.