Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Comirnaty 3 micrograms/dose concentrate for dispersion for injection

COVID-19 mRNA Vaccine (nucleoside modified)

Tozinameran

PLGB 53632/0008

BioNTech Manufacturing GmbH

LAY SUMMARY

Comirnaty 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)
Tozinameran

This is a summary of the Public Assessment Report (PAR) for Comirnaty 3 micrograms/dose concentrate for dispersion for injection. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Comirnaty 3 micrograms/dose Vaccine in this lay summary for ease of reading.

For practical information about using Comirnaty 3 micrograms/dose Vaccine, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Comirnaty 3 micrograms/dose Vaccine and what is it used for?
This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 20 October 2022 (EMEA/H/C/005735/X/0138), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

Comirnaty 3 micrograms/dose Vaccine is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to infants and children from 6 months to 4 years of age.

The application is a line extension of the existing product, Comirnaty 30 micrograms/dose concentrate for dispersion for injection (PLGB 53632/0002).

How does Comirnaty 3 micrograms/dose Vaccine work?
The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

How is Comirnaty 3 micrograms/dose Vaccine used?
The pharmaceutical form of this medicine is a concentrate for dispersion for injection and the route of administration is intramuscular (into the muscle).

Comirnaty 3 micrograms/dose Vaccine is given after dilution as an injection of 0.2 mL into a muscle of the thigh in infants from 6 to less than 12 months of age.

In infants and children 1 year of age or older, Comirnaty 3 micrograms/dose Vaccine is given after dilution as an injection of 0.2 mL into a muscle of the thigh or into a muscle of the upper arm.

The child will receive 3 injections.

It is recommended to receive the second dose of the same vaccine 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the vaccination course.

If a child turns 5 years old between their doses in the vaccination course, he/she should complete the series at the same 3 micrograms dose level.

For further information on how Comirnaty 3 micrograms/dose Vaccine is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Comirnaty 3 micrograms/dose Vaccine can only be obtained with a prescription.

The individual should ask the administering healthcare practitioner if they have any questions concerning the vaccine.

What benefits of Comirnaty 3 micrograms/dose Vaccine have been shown in studies?
A main study in children from 6 months to 4 years of age evaluated the immune response triggered by the vaccine (given as 3 injections) by measuring the level of antibodies against SARS-CoV-2. The study showed that the immune response was comparable to that seen with a higher dose of Comirnaty (30 micrograms), given as two injections to 16- to 25-year-olds.

What are the possible side effects of Comirnaty 3 micrograms/dose Vaccine?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Comirnaty 3 micrograms/dose Vaccine (which may affect more than 1 in 10 people) are irritability (6 months to < 2 years); injection site: pain/tenderness, swelling; tiredness; headache; drowsiness (6 months to <2 years); muscle pain; chills; joint pain; diarrhoea; and fever.

Why was Comirnaty 3 micrograms/dose Vaccine approved?
MHRA decided that the benefits are greater than the risks and recommended that this vaccine can be approved for use.

Comirnaty 3 micrograms/dose Vaccine has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Comirnaty 3 micrograms/dose Vaccine?"

What measures are being taken to ensure the safe and effective use of Comirnaty 3 micrograms/dose Vaccine?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Comirnaty 3 micrograms/dose Vaccine. The RMP details the important risks of Comirnaty 3 micrograms/dose Vaccine, how these risks can be minimised, any uncertainties about Comirnaty 3 micrograms/dose Vaccine (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Comirnaty 3 micrograms/dose Vaccine:

Important Identified Risks	Myocarditis and Pericarditis
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

An additional risk minimisation measure to address myocarditis and pericarditis is a Direct Healthcare Professional Communication (DHPC) to ensure that healthcare providers (HCPs) are aware of the potential for myocarditis and pericarditis associated with COVID-19 mRNA vaccine use.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Comirnaty 3 micrograms/dose Vaccine are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Comirnaty 3 micrograms/dose Vaccine
A marketing authorisation was granted in Great Britain on 05 December 2022.

The full PAR for Comirnaty 3 micrograms/dose Vaccine follows this summary.

This summary was last updated in January 2023.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Comirnaty 3 micrograms/dose concentrate for dispersion for injection (PLGB 53632/0008) could be approved.

The product is approved for the following indications:
For active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years. The use of this vaccine should be in accordance with official recommendations.

The active substance in this product is tozinameran. Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non replicating RNA into host cells to direct transient expression of the SARS CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 20 October 2022 (EMEA/H/C/005735/X/0138), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended). The application is a line extension of the existing product, Comirnaty 30 micrograms/dose concentrate for dispersion for injection (PLGB 53632/0002).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100392-PIP01-21-M01. The applicant has made a post-marketing commitment to submit a PIP modification.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 24 November 2022. A marketing authorisation was granted on 05 December 2022.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for this application is satisfactory.
The grant of a marketing authorisation is recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.
The grant of a marketing authorisation is recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for this application is satisfactory.
The grant of a marketing authorisation is recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance and risk minimisation measures have been proposed:

Important Identified Risk: Myocarditis and Pericarditis

Evidence for linking the risk to the medicine	Events of Myocarditis and Pericarditis have been reported.
Risk factors and risk groups	Post-authorization reports have been reported more frequently in adolescent and young adult male patients following the second dose of vaccine; however, reports have been received for adult males and females of broader age range and following the first vaccination also.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4. and 4.8. Additional risk minimisation measures: DHCP letter and communication plan
Additional pharmacovigilance activities	• C4591009 • C4591011 • C4591012 • C4591021 (former ACCESS/VAC4EU) • C4591038 (former C4591021 sub-study) • C4591036 (former Pediatric Heart Network study) See Section II.C this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED) including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Evidence for linking the risk to the medicine	VAED is considered a potential risk because it has not been seen in human studies with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus. VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease.
Risk factors and risk groups	It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	C4591001 C4591007 C4591009[a] C4591011[a] C4591012[a] C4591021 (former ACCESS/VAC4EU)[a] See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Addresses AESI-based safety events of interest including vaccine associated enhanced disease

Missing Information: Use in Pregnancy and while Breast Feeding

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6; PL section 2. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	• C4591009[a] • C4591010[a] • C4591011[a] • C4591015 • C4591021 (former ACCESS/VAC4EU)[a] • C4591022[a] See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Please note that studies C4591009, C4591010, C4591011, C4591021 (former ACCESS/VAC4EU) and C4591022 address only "Use in pregnancy" and not "Breast feeding".

Missing Information: Use in Immunocompromised Patients

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	• BNT162-01 cohort 13 • C4591010[a] • C4591011 • C4591012 • C4591021 (former ACCESS/VAC4EU) • C4591024 (former Safety and Immunogenicity in high-risk adults) See Section II.C of this summary for an overview of the post-authorisation development plan.

a. Addresses AESI-based safety events of interest

Missing Information: Use in Frail Patients with Co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	• C4591001 subset • C4591011 • C4591012 • C4591021 (former ACCESS/VAC4EU) • C4591024 (former Safety and immunogenicity in high-risk adults) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	• C4591011 • C4591012 • C4591021 (former ACCESS/VAC4EU) • C4591024 (former Safety and immunogenicity in high-risk adults) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Interaction with other Vaccines

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	• C4591030 (Co-administration study with seasonal influenza vaccine) See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Long Term Safety Data

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	• C4591001 • C4591007 • C4591010 • C4591011 • C4591012 • C4591021 (former ACCESS/VAC4EU) • C4591038 (former C4591021 substudy) • C4591036 (former PHN) See Section II.C of this summary for an overview of the post-authorisation development plan.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Comirnaty 30 micrograms/dose concentrate for dispersion for injection (EMEA/H/C/005735). The bridging report submitted by the applicant is acceptable.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

Comirnaty 3 micrograms/dose Vaccine has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. The Marketing Authorisation Holder (MAH) shall complete, within the stated timeframe, the following measures:

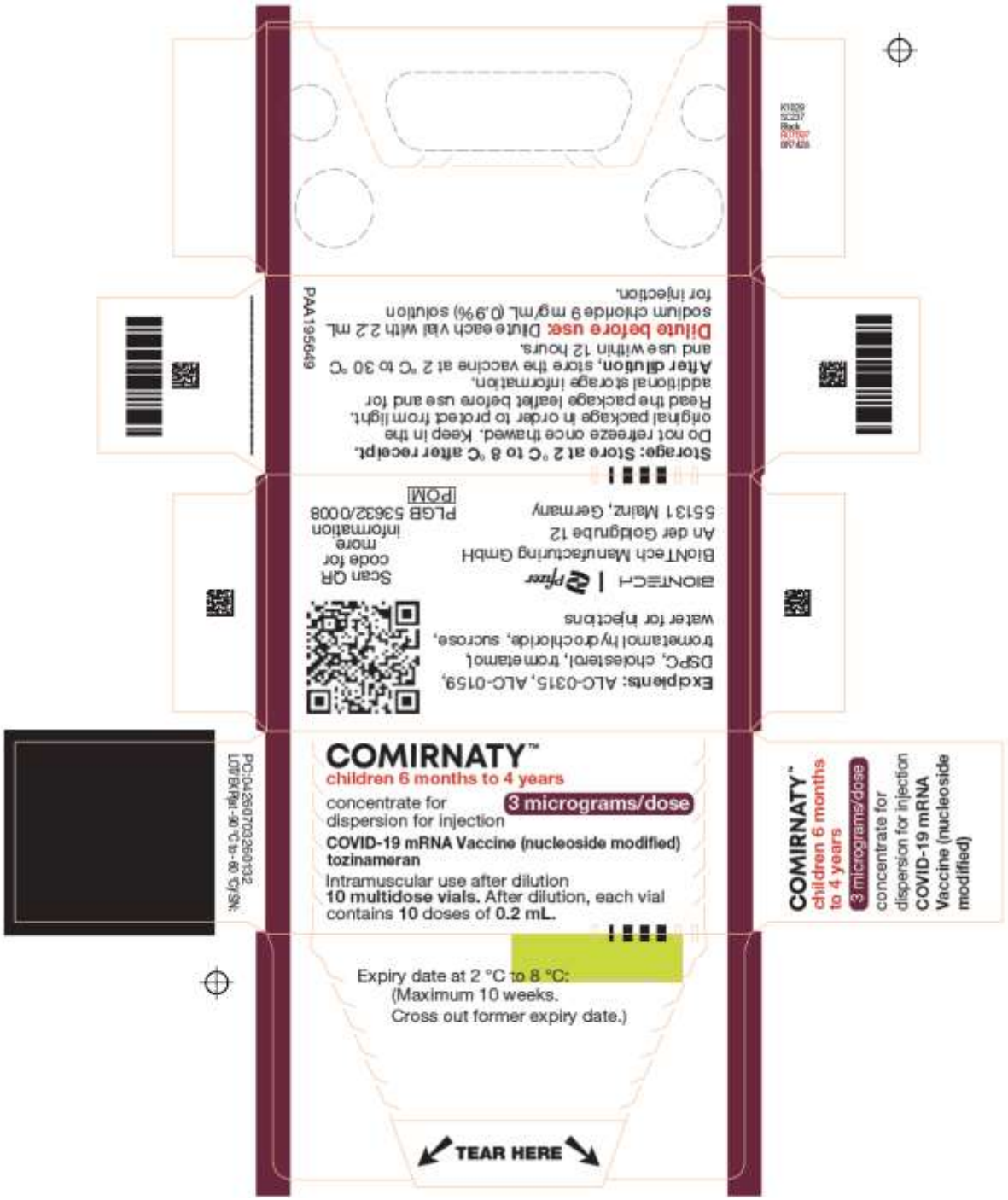
Description	Due date
1. The MAH should submit a stand-alone Summary Safety Report for the product approved in children aged 6 months to 4 years, including a comprehensive review of vaccination errors, with the data lock point falling 3 months after the date of approval in Great Britain.	05/03/2023
2. In the post-approval studies to be updated to include children aged 6 months to 4 years, the MAH is requested to examine the frequency, nature and severity of vaccination errors and medically-attended fever, and interactions with other vaccines relevant to this age group in the UK (within 2 months of approval).	05/02/2023
3. The MAH should clarify if people aged 6 months to 4 years can be included in the UK study of post-authorisation vaccine effectiveness (study WI255886), providing an updated protocol, or make a new proposal for studying vaccine effectiveness in this population in the UK (within one month of approval).	05/01/2023
4. According to the study protocol of study C4591007, an updated efficacy analysis at the end of the blinded follow-up period is planned. The MAH should provide complete safety and persistence-of-immunogenicity analysis after complete data are available in each age group or at the end of the study. Interim analysis, 6 months post	03/12/2024

dose 3 immunogenicity and safety data will be presented. The final report for the supportive vaccine efficacy analysis should be also submitted by the MAH when ready.	

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.



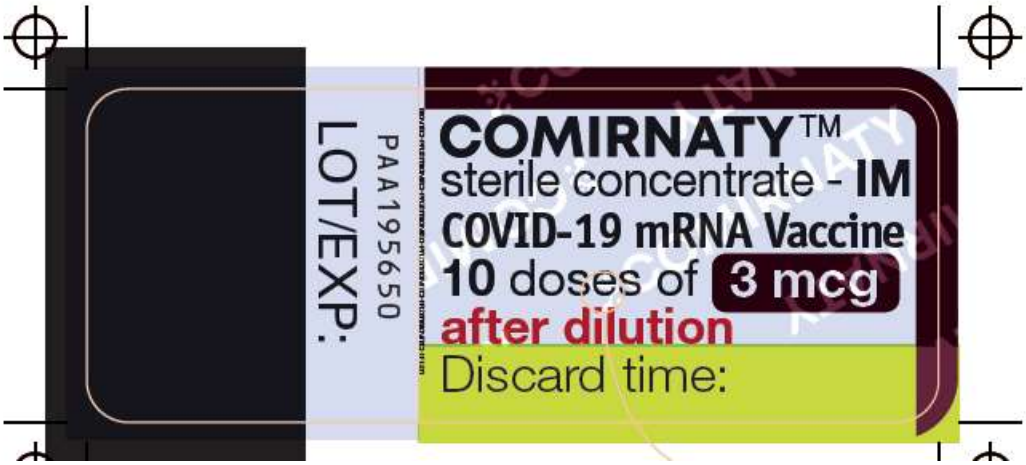

LOT/EXP:
PAA195650
COMIRNATY™
sterile concentrate - IM
COVID-19 mRNA Vaccine
10 doses of 3 mcg
after dilution
Discard time:

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**