REG 174 INFORMATION FOR UK HEALTHCARE PROFESSIONALS

This medicinal product has been given authorisation for temporary supply by the UK Department of Health and Social Care and the Medicines & Healthcare products Regulatory Agency. It does not have a marketing authorisation, but this temporary authorisation grants permission for the medicine to be used for active immunization to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals aged 16 years of age and over.

As with any new medicine in the UK, this product will be closely monitored to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial and must be diluted before use. 1 vial (0.45 mL) contains 5 doses of 30 micrograms of BNT162b2 RNA (embedded in lipid nanoparticles).

COVID-19 mRNA Vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

Excipients with known effect:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection.
The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of COVID-19 mRNA Vaccine BNT162b2 should be in accordance with official guidance.

4.2 Posology and method of administration

Posology
Individuals 16 years of age and older
COVID-19 mRNA Vaccine BNT162b2 is administered intramuscularly after dilution as a series of two doses (0.3 mL each) at least 21 days apart (see section 5.1).

There are no data available on the interchangeability of COVID-19 mRNA Vaccine BNT162b2 with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of COVID-19 mRNA Vaccine BNT162b2 should receive a second dose of COVID-19 mRNA Vaccine BNT162b2 to complete the vaccination series.

Individuals may not be maximally protected until at least 7 days after their second dose of the vaccine.

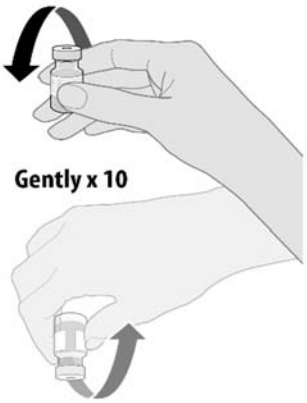
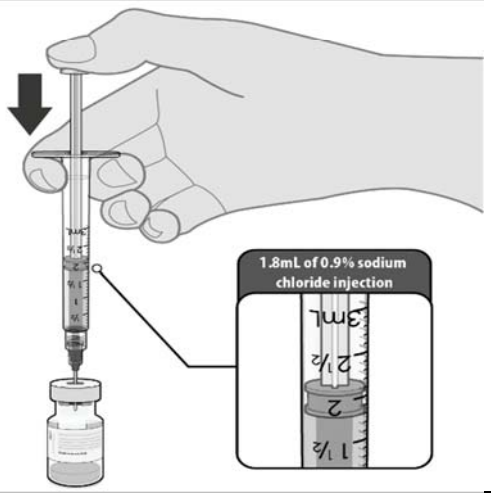
For further information on efficacy, see section 5.1.

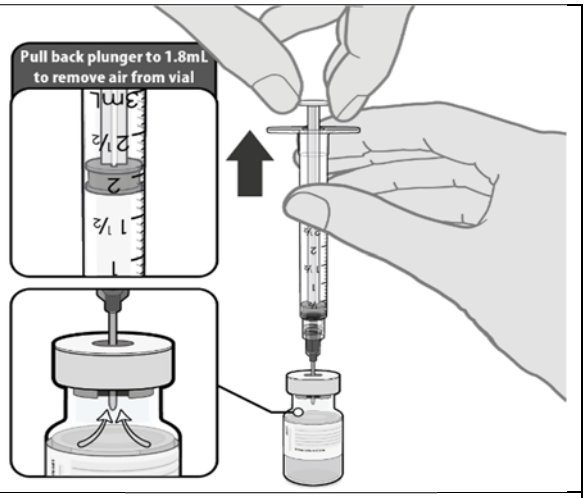
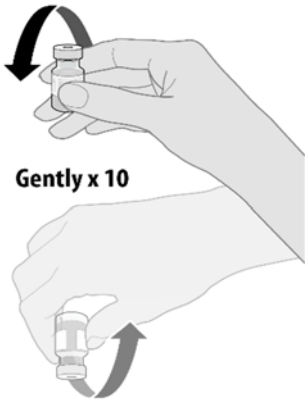
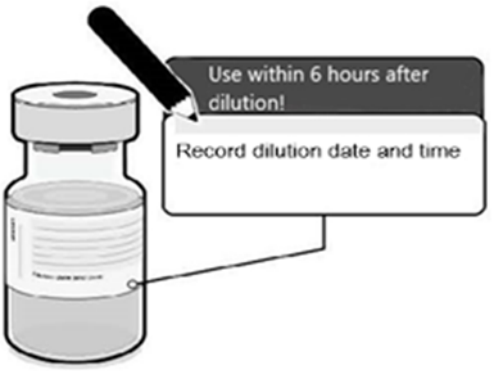
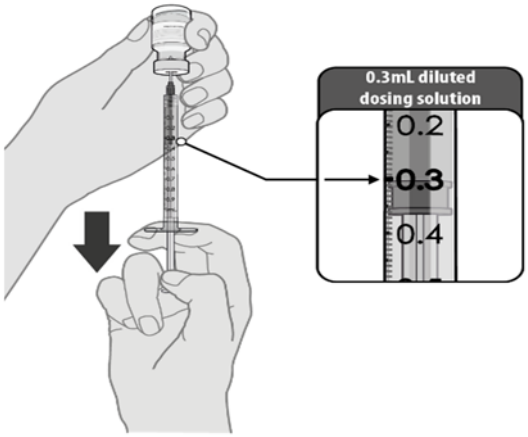
Paediatric population
The safety and efficacy of COVID-19 mRNA Vaccine BNT162b2 in children under 16 years of age have not yet been established.

Method of administration
Administer the COVID-19 mRNA Vaccine BNT162b2 vaccine intramuscularly in the deltoid muscle after dilution.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

Preparation: The multidose vial is stored frozen and must be thawed prior to dilution.

Frozen vials should be transferred to 2 °C to 8 °C to thaw. Alternatively, frozen vials may also be thawed and kept at temperatures up to 25 °C for a maximum of two hours in preparation for dilution for use. When removed from the freezer, the undiluted vaccine has a maximum shelf life of up to 5 days (120 hours) at 2 °C to 8 °C and an additional 2 hours at temperatures up to 25 °C in preparation for dilution.	
When the thawed vial is at room temperature gently invert 10 times prior to dilution. **Do not shake**. Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.	
The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and **aseptic** techniques. **Warning:** Unpreserved sodium chloride 9 mg/mL (0.9%) solution for injection is the **only** diluent that should be used. This diluent is not provided in the vaccine carton.	

Equalise vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.	
Gently invert the diluted solution 10 times. **Do not shake.**	
The diluted vaccine should present as an off-white solution with no particulates visible. Discard the diluted vaccine if particulates or discolouration are present.	
The diluted vials should be marked with the dilution date and time and stored between 2 °C to 25 °C. Use as soon as practically possible, and within 6 hours after dilution.	
After dilution, the vial contains 5 doses of 0.3 mL. Withdraw the required 0.3 mL dose of diluted vaccine using a sterile needle and syringe and administer. Vial volume was optimized to reliably obtain 5 doses regardless of syringe type used as most syringe and needle combinations require withdrawal of excess volume in order to ensure the full 0.3 mL dose of vaccine can be administered. When low dead-volume syringes and/or needles are used, the amount remaining in the vial after 5 doses have been extracted may be sufficient for an additional (sixth) dose. Care should be taken to	

ensure a full 0.3 mL will be administered to the subject and that all doses from a single prepared vial are administered within 6 hours of the time of dilution. Where a full 0.3 mL dose cannot be extracted the contents should be discarded. Any unused vaccine should be discarded 6 hours after dilution. The vaccine should not be shipped (transported) by motor vehicle after dilution away from the site of dilution. Any shipping (transportation) by motor vehicle after dilution of the vial is at the risk of the Health Care Professional.	

For instructions on disposal see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity and anaphylaxis
Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.
Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of the COVID-19 mRNA Vaccine BNT162b2.

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

General recommendations

The administration of COVID-19 mRNA Vaccine BNT162b2 should be postponed in individuals suffering from acute severe febrile illness.

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine. No data are available about concomitant use of immunosuppressants.

As with any vaccine, vaccination with COVID-19 mRNA Vaccine BNT162b2 may not protect all vaccine recipients.

No data are available on the use of COVID-19 mRNA Vaccine BNT162b2 in persons that have previously received a full or partial vaccine series with another COVID-19 vaccine.

Excipient information
This vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially ‘potassium-free’.
This vaccine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of COVID-19 mRNA Vaccine BNT162b2 with other vaccines has not been studied (see section 5.1).

Do not mix COVID-19 mRNA Vaccine BNT162b2 with other vaccines/products in the same syringe.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited experience with use of the COVID-19 mRNA Vaccine BNT162b2in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of the COVID-19 mRNA Vaccine BNT162b2 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding
It is unknown whether the COVID-19 mRNA Vaccine BNT162b2 is excreted in human milk.

Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3)

4.7 Effects on ability to drive and use machines

COVID-19 mRNA Vaccine BNT162b2 has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile
The safety of COVID-19 mRNA Vaccine BNT162b2 was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) enrolled approximately 44,000 participants, 12 years of age or older. In Study 2, a total of 21,720 participants 16 years of age or older received at least one dose of COVID-19 mRNA Vaccine BNT162b and 21,728 participants 16 years of age or older received placebo. Out of these, at the time of the analysis, 19,067 (9531 COVID-19 mRNA Vaccine BNT162b2 and 9536 placebo) were evaluated for safety 2 months after the second dose of COVID-19 mRNA Vaccine BNT162b2.

Demographic characteristics were generally similar with regard to age, gender, race and ethnicity among participants who received COVID-19 mRNA Vaccine and those who received placebo. Overall, among the participants who received COVID-19 mRNA Vaccine BNT162b2, 51.5% were male and 48.5% were female, 82.1% were White, 9.6% were Black or African American, 26.1% were Hispanic/Latino, 4.3% were Asian and 0.7% were Native American/Alaskan native.

The most frequent adverse reactions in participants 16 years of age and older were pain at the injection site (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 30%), chills (> 30%), arthralgia (> 20%) and pyrexia (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. If required, symptomatic treatment with analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used.

Adverse reactions from clinical studies
Adverse reactions reported in clinical studies are listed in this section per MedDRA system organ class, in decreasing order of frequency and seriousness. The frequency is defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from available data).

Blood and lymphatic system disorders
Uncommon: Lymphadenopathy

Immune system disorders
Not Known: Anaphylaxis; hypersensitivity

Nervous system disorders
Very common: Headache
Rare: Acute peripheral facial paralysis[†]

Musculoskeletal and connective tissue disorders
Very common: Arthralgia; myalgia

General disorders and administration site conditions
Very common: Injection-site pain; fatigue; chills; pyrexia
Common: Redness at injection site; injection site swelling
Uncommon: Malaise

Gastrointestinal disorders
Common Nausea

[†]Throughout the safety follow-up period to date, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

Reporting of suspected adverse reactions
If you are concerned about an adverse event, it should be reported on a Yellow card. Reporting forms and information can be found at https://coronavirus-yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store and include the vaccine brand and batch/Lot number if available.
Alternatively, adverse events of concern in association with Pfizer BioNTech COVID-19 mRNA vaccine BNT 162b2 can be reported to Pfizer Medical Information on 01304 616161 or via www.pfizersafetyreporting.com.
Please do not report the same adverse event(s) to both systems as all reports will be shared between Pfizer and MHRA (in an anonymized form) and dual reporting will create unnecessary duplicates.

4.9 Overdose

Participants who received 58 micrograms of COVID-19 mRNA Vaccine in clinical trials did not report an increase in reactogenicity or adverse events.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACODYNAMIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group}, ATC code: not yet assigned

Mechanism of action

The nucleoside-modified messenger RNA in COVID-19 mRNA Vaccine BNT162b2 is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19 disease.

Efficacy in participants 16 years of age and older

The efficacy of COVID-19 mRNA Vaccine BNT162b2 was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa and South America. Study 1 enrolled 60 participants, 18 through 55 years of age. Study 2 is a multicentre, placebo-controlled efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19 disease. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). There was no requirement for prophylactic use of paracetamol or analgesics. Influenza vaccines could be administered outside a window ± 14 days of the vaccine doses.

In Study 2, approximately 44,000 participants 12 years of age and older were randomised equally and received 2 doses of COVID-19 mRNA Vaccine or placebo with a planned interval of 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19 disease.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

Demographic characteristics were generally similar with regard to age, gender, race and ethnicity among participants who received COVID-19 mRNA BNT162b2 vaccine and those who received placebo. Overall, among the participants who received COVID-19 mRNA vaccine, 51.1% were male and 48.9% were female, 82.8% were White, 8.9% were Black or African American, 26.8% were Hispanic/Latino, 4.5% were Asian and 0.6% were Native American/Alaskan native. 57.2% were aged 16-55 years, 42.6% were aged > 55 years and 21.8% were ≥ 65 years.

Efficacy against COVID-19 disease

At the time of the analysis of Study 2, information presented is based on participants 16 years and older. Participants had been followed for symptomatic COVID-19 disease for at least 2,214 person-years for the COVID-19 mRNA Vaccine and at least 2,222 person-years in the placebo group. There were 8 confirmed COVID-19 cases identified in the COVID-19 mRNA Vaccine group and 162 cases in the placebo group, respectively. In this analysis, compared to placebo, efficacy of COVID-19 mRNA Vaccine BNT162b2 from first COVID-19 occurrence from 7 days after Dose 2 in participants **without evidence** of prior infection with SARS-CoV-2 was 95.0% (95% credible interval of 90.3% to 97.6%). In participants 65 years of age and older and 75 years of age and older without evidence of prior infections with SARS-CoV-2, efficacy of COVID-19 mRNA Vaccine BNT162b2 was 94.7%

(two-sided 95% confidence interval of 66.7% to 99.9%) and 100% (two-sided 95% confidence interval of -13.1% to 100.0%) respectively.

In a separate analysis, compared to placebo, efficacy of COVID-19 mRNA Vaccine from first COVID-19 occurrence from 7 days after Dose 2 in participants **with or without evidence** of prior infection with SARS-CoV-2 was 94.6% (95% credible interval of 89.9% to 97.3%).

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 disease including those with one or more comorbidities that increase the risk of severe COVID-19 disease (e.g. asthma, BMI ≥ 30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 disease.*

**Case definition (at least 1 of): fever, new or increased cough, new or increased shortness of breath; chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.*

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity.
Reproductive toxicity
Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered with the COVID-19 mRNA Vaccine BNT162b2 prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No data on the COVID-19 mRNA Vaccine BNT162b2 are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

This vaccine contains polyethylene glycol/macrogol (PEG) as part of ALC-0159.

ALC-0315 = (4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate),
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide,
1,2-Distearoyl-sn-glycero-3-phosphocholine,
cholesterol,
potassium chloride,
potassium dihydrogen phosphate,
sodium chloride,
disodium hydrogen phosphate dihydrate,
sucrose,
water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

6 months at -80 °C to -60 °C.

6.4 Special precautions for storage

Store in a freezer at -80 °C to -60 °C.
Store in the thermal container at -90 ºC to -60 ºC.

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

Once removed from the freezer, the undiluted vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours at temperatures up to 25 °C, prior to use. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 25 °C and use as soon as practically possible and within 6 hours. The vaccine does not contain a preservative. Discard any unused vaccine.

Once diluted, the vials should be marked with the dilution time and discarded within 6 hours of dilution.

Once thawed, the vaccine cannot be re-frozen.

6.5 Nature and contents of container

Concentrate for solution for injection for 5 doses in a 2 mL clear vial (type I glass) with a stopper (bromobutyl) and a flip-off plastic cap with aluminium seal.

Pack size: 195 vials

6.6 Special precautions for disposal and other handling

When removed from the freezer, the vaccine has a maximum possible shelf life of up to 5 days when stored at 2-8 ºC (label to be added once box removed from freezer). A 195 vial pack may take 3 hours to thaw at 2-8ºC.

The product can alternatively be defrosted and kept for up to 2 hours at up to 25 ºC before being diluted for use. This facilitates immediate thaw and use when removed directly from the freezer to 25 ºC. In this instance the product is to be diluted within 2 hours of removing from the freezer.

Once thawed, the vaccine cannot be refrozen.

After dilution the vaccine should be used as soon as is practically possible and within 6 hours of dilution; it can be stored at 2-25 ºC during this period. From a microbiological point of view, it would not normally be considered good practice to store a diluted product for 6 hours at 25 ºC before being administered. The product would ideally be used as soon as practically possible after dilution.

The vaccine does not contain a preservative. Discard any unused vaccine.

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

For instructions on dose preparation of the medicinal product before administration, see section 4.2.

7. MARKETING AUTHORISATION HOLDER

Not applicable.

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

December 2020