ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Spikevax dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial which contains 10 doses of 0.5 mL.

One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection
White to off white dispersion (pH: 7.0 – 8.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older
Spikevax is administered as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose (see sections 4.4 and 5.1).

There are no data available on the interchangeability of Spikevax with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of Spikevax should receive the second dose of Spikevax to complete the vaccination course.

Paediatric population
The safety and efficacy of Spikevax in children and adolescents less than 12 years of age have not yet been established. No data are available.

Elderly population
No dosage adjustment is required in elderly individuals ≥65 years of age.

Method of administration

The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity and anaphylaxis

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

Close observation for at least 15 minutes is recommended following vaccination. The second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Spikevax.

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

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

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Spikevax may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

Individuals may not be fully protected until 14 days after their second dose. As with all vaccines, vaccination with Spikevax may not protect all vaccine recipients.

Excipients with known effect

Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per 0.5 mL dose, that is to say, essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Spikevax with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of Spikevax in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of Spikevax 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 Spikevax 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

Spikevax has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Participants 18 years of age and older

The safety of Spikevax was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical study conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of Spikevax (n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older.

The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

Overall, there was a higher incidence of some adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.

Adolescents 12 through 17 years of age

Safety data for Spikevax in adolescents were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical study conducted in the United States involving 3,726 participants 12 through 17 years of age who received at least one dose of Spikevax (n=2,486) or placebo (n=1,240) (NCT04649151). Demographic characteristics were similar among participants who received Spikevax and those who received placebo.

The most frequent adverse reactions in adolescents 12 to 17 years of age were injection site pain (97%), headache (78%), fatigue (75%), myalgia (54%), chills (49%), axillary swelling/tenderness (35%), arthralgia (35%), nausea/vomiting (29%), injection site swelling (28%), injection site erythema (26%), and fever (14%).

Tabulated list of adverse reactions from clinical studies and post authorisation experience in individuals 12 years of age and older
The safety profile presented below is based on data generated in a placebo- controlled clinical study on 30,351 adults ≥ 18 years of age, another placebo-controlled clinical study with 3,726 participants 12 through 17 years of age, and post-marketing experience. Differences between the 2 studies are denoted by footnotes below the table.

Adverse reactions reported are listed according to the following frequency convention:

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 the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness (Table 1).

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

MedDRA system organ class	Frequency	Adverse reaction(s)
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
	Rare	Acute peripheral facial paralysis** Hypoaesthesia
Cardiac disorders	Not known	Myocarditis Pericarditis
Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills Pyrexia Injection site swelling
	Common	Injection site erythema Injection site urticaria Injection site rash Delayed injection site reaction
	Uncommon	Injection site pruritus
	Rare	Facial swelling***

*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site. Other lymph nodes (e.g., cervical, supraclavicular) were affected in some cases.
**Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the Spikevax group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.
***There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination.

The reactogenicity and safety profile in 343 subjects receiving Spikevax, that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

4.9 Overdose

No case of overdose has been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, other viral vaccines, ATC code: J07BX03

Mechanism of action

Spikevax contains mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into viral protein. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The expressed, membrane-bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralising antibodies, which may contribute to protection against COVID-19.

Clinical efficacy in adults

The adult study was a randomised, placebo-controlled, observer-blind Phase 3 clinical study (NCT04470427) that excluded individuals who were immunocompromised or had received immunosuppressants within 6 months, as well as participants who were pregnant, or with a known history of SARS-CoV-2 infection. Participants with stable HIV disease were not excluded. Influenza vaccines could be administered 14 days before or 14 days after any dose of Spikevax. Participants were also required to observe a minimum interval of 3 months after receipt of blood/plasma products or immunoglobulins prior to the study in order to receive either placebo or Spikevax.

A total of 30,351 subjects were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease.

The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28,207 subjects who received either Spikevax (n=14,134) or placebo (n=14,073) and had a negative baseline SARS-CoV-2 status. The PPS study population included 47.4% female, 52.6% male, 79.5% White, 9.7% African American, 4.6% Asian, and 6.2% other. 19.7% of participants identified as Hispanic or Latino. The median age of subjects was 53 years (range 18-94). A dosing window of –7 to +14 days for administration of the second dose (scheduled at day 29) was allowed for inclusion in the PPS. 98% of vaccine recipients received the second dose 25 days to 35 days after dose 1 (corresponding to -3 to +7 days around the interval of 28 days).

COVID-19 cases were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT PCR) and by a Clinical Adjudication Committee. Vaccine efficacy overall and by key age groups are presented in Table 2.

Table 2: Vaccine efficacy analysis: confirmed COVID-19[#] regardless of severity starting 14 days after the 2nd dose – per-protocol set

Age group (years)	Spikevax			Placebo			
	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Subjects N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	% Vaccine efficacy (95% CI)*
Overall (≥18)	14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)**
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)
≥65 to <75	2,953	4	5.586	2,864	22	31.744	82.4% (48.9, 93.9)
≥75	630	0	0	688	7	41.968	100% (NE, 100)

[#]COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose.
*Vaccine efficacy and 95% confidence interval (CI) from the stratified Cox proportional hazard model
** CI not adjusted for multiplicity. Multiplicity adjusted statistical analyses were carried out in an interim analysis based on less COVID-19 cases, not reported here.

Among all subjects in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 of 185 (16%) cases reported in the placebo group. Of the 30 participants with severe disease, 9 were hospitalised, 2 of which were admitted to an intensive care unit. The majority of the remaining severe cases fulfilled only the oxygen saturation (SpO2) criterion for severe disease (≤ 93% on room air).

The vaccine efficacy of Spikevax to prevent COVID-19, regardless of prior SARS-CoV-2 infection (determined by baseline serology and nasopharyngeal swab sample testing) from 14 days after Dose 2 was 93.6% (95% confidence interval 88.5, 96.4%).

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Clinical efficacy in adolescents 12 through 17 years of age

The adolescent study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical study (NCT04649151) to evaluate the safety, reactogenicity, and efficacy of Spikevax in adolescents 12 to 17 years of age. Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 3,732 participants were randomised 2:1 to receive 2 doses of Spikevax or saline placebo 1 month apart.

A secondary efficacy analysis was performed in 3,181 participants who received 2 doses of either Spikevax (n=2,139) or placebo (n=1,042) and had a negative baseline SARS-CoV-2 status in the Per Protocol Set. Between participants who received Spikevax and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose.

There were zero symptomatic COVID-19 cases in the Spikevax group and 4 symptomatic COVID-19 cases in the placebo group.

Immunogenicity in adolescents 12 to 17 years of age

A non-inferiority analysis evaluating SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 was conducted in the Per-Protocol immunogenicity subsets of adolescents aged 12 through 17 (n=340) in the adolescent study and in participants aged 18 through 25 (n=296) in the adult study. Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The geometric mean ratio (GMR) of the neutralising antibody titers in adolescents 12 to 17 years of age compared to the 18- to 25-year-olds was 1.08 (95% CI: 0.94, 1.24). The difference in seroresponse rate was 0.2% (95% CI: -1.8, 2.4). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% of the seroresponse rate difference > -10%) were met.

Elderly population

Spikevax was assessed in individuals 12 years of age and older, including 3,768 subjects 65 years of age and older. The efficacy of Spikevax was consistent between elderly (≥65 years) and younger adult subjects (18-64 years).

Paediatric population

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

Conditional approval

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

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity
General toxicity studies were conducted in rats (intramuscularly receiving up to 4 doses exceeding the human dose once every 2 weeks). Transient and reversible injection site oedema and erythema and transient and reversible changes in laboratory tests (including increases in eosinophils, activated partial thromboplastin time, and fibrinogen) were observed. Results suggests the toxicity potential to humans is low.

Genotoxicity/carcinogenicity
In vitro and in vivo genotoxicity studies were conducted with the novel lipid component SM-102 of the vaccine. Results suggests the genotoxicity potential to humans is very low. Carcinogenicity studies were not performed.

Reproductive toxicity
In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of Spikevax was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in maternal

animals from prior to mating to the end of the study on lactation day 21 as well as in foetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo foetal or offspring development or postnatal development. No data are available of Spikevax vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lipid SM-102 (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate)
Cholesterol
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG)
Trometamol
Trometamol hydrochloride
Acetic acid
Sodium acetate trihydrate
Sucrose
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial:
7 months at -25ºC to -15ºC.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days. Within this period, up to 12 hours may be used for transportation.

Once thawed the vaccine should not be re-frozen.

The unopened vaccine may be stored at 8°C to 25°C up to 24 hours after removal from refrigerated conditions.

Punctured vial:
Chemical and physical in-use stability has been demonstrated for 19 hours at 2°C to 25ºC after initial puncture (within the allowed use period of 30 days at 2°C to 8ºC and 24 hours at 8°C to 25ºC). From a microbiological point of view, the product should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store frozen between -25ºC to -15ºC.
Store in the original carton to protect from light.
Do not store on dry ice or below -50ºC.
For storage conditions after thawing and first opening see section 6.3.

Transportation of thawed vials in liquid state at 2°C to 8°C
If transport at -50°C to -15°C is not feasible, available data support transportation of one or more thawed vials in liquid state for up to 12 hours at 2°C to 8°C (within the 30 days shelf life at 2°C to 8°C). Once thawed and transported in liquid state at 2°C to 8°C, vials should not be refrozen and should be stored at 2°C to 8°C until use.

6.5 Nature and contents of container

5 ml dispersion in a vial (type 1 or type 1 equivalent glass) with a stopper (chlorobutyl rubber) and a flip-off plastic cap with seal (aluminium seal).

Each vial contains 10 doses of 0.5 mL.

Pack size: 10 multidose vials

6.6 Special precautions for disposal and other handling

The vaccine should be prepared and administered by a trained healthcare professional using aseptic techniques to ensure sterility of the dispersion.

The vaccine comes ready to use once thawed.

Do not shake or dilute. Swirl the vial gently after thawing and before each withdrawal.

Spikevax vials are multidose.

Ten (10) doses (of 0.5 mL each) can be withdrawn from each vial. Pierce the stopper preferably at a different site each time.

An additional overfill is included in each vial to ensure that 10 doses of 0.5 mL can be delivered.

Thawed vials and filled syringes can be handled in room light conditions.

Frozen Storage

Store frozen between –25° to –15°C
Do not store on dry ice or below -50°C
Store in the original carton to protect from light.

Thaw Each Vial Before Use

Vial images for illustrative purposes only

2 hours and 30 minutes in refrigerator

2° to 8°C
(within the 30 days shelf life at 2° to 8°C)

OR

1 hour at room temperature

15° to 25°C

Let vial sit at room temperature for 15 minutes before administering

Instructions Once Thawed

Unpunctured Vial

Maximum times

30 days — Refrigerator — 2° to 8°C

24 hours — Cool storage up to room temperature — 8° to 25°C

After first dose has been withdrawn

Maximum time

19 hours — Refrigerator or room temperature

Vial should be held between 2° to 25°C. Record the date and time of discard on the vial label.

Discard punctured vial after 19 hours.

Withdraw each 0.5 mL dose of vaccine from the vial using a new sterile needle and syringe for each injection to prevent transmission of infectious agents from one person to another. **The dose in the syringe should be used immediately.**

Once the vial has been punctured to withdraw the initial dose, the vaccine should be used immediately and be discarded after 19 hours.

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

NEVER refreeze thawed vaccine

Administration

Swirl vial gently after thawing and before each withdrawal.
The vaccine comes ready to use once thawed. **Do not shake or dilute.**

Prior to injection, inspect each dose to:

Confirm liquid is **white to off-white** in colour in both vial and syringe.

Verify syringe volume of **0.5 mL**.

The COVID-19 Vaccine Moderna may contain white or translucent product-related particulates.

If dosage is incorrect, or discolouration and other particulate matter is present, do not administer the vaccine.

7. MARKETING AUTHORISATION HOLDER

MODERNA BIOTECH SPAIN, S.L.
Calle Monte Esquinza 30
28010 Madrid
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1507/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 January 2021

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

LONZA AG
Lonzastrasse 2
Visp 3930
Switzerland

LONZA AG
Ibex Solutions
Rottenstrasse 6
Visp 3930
Switzerland

ModernaTX, Inc.
One Moderna Way
Norwood, MA 02062
USA

Lonza Biologics, Inc.
101 International Drive Portsmouth, NH 03801
USA

Name and address of the manufacturer responsible for batch release

Rovi Pharma Industrial Services, S.A.
Paseo de Europa, 50
28703. San Sebastián de los Reyes
Madrid, Spain

Recipharm Monts
18 Rue de Montbazon
Monts, France 37260

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 July 2022. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 July 2022 at the latest, in line with the agreed plan for this transfer of testing.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

Official batch release

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic safety update reports (PSURs)

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

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

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

Risk management plan (RMP)

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

An updated RMP should be submitted:

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

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

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

Description	Due date
In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data.	31 July 2021
In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the MAH should provide additional comparability and validation data.	15 November 2021
In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience.	15 July 2021
In order to confirm the efficacy and safety of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P301.	December 2022
In order to confirm the efficacy and safety of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P203, including the full bioanalytical report.	30 September 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Spikevax dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each multidose vial contains 10 doses (0.5 mL each).

3. LIST OF EXCIPIENTS

Excipients: Lipid SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG), trometamol, trometamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Read the package leaflet before use.

Scan here for package leaflet or visit www.modernacovid19global.com.

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

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen at -25°C to -15°C.
Read the package leaflet for the shelf life after first opening and for additional storage information.
Keep the vial in the outer carton to protect from light

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

Dispose of in accordance with local requirement.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MODERNA BIOTECH SPAIN, S.L.
Calle Monte Esquinza, 30
28010 Madrid
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1507/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Spikevax dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)
IM

2. METHOD OF ADMINISTRATION

Intramuscular use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Multidose vial
(10 doses of 0.5 mL)

6. OTHER

Scan here for package leaflet or visit www.modernacovid19global.com.
Discard date/time:

ANNEX III

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Spikevax dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

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

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spikevax is and what it is used for

Spikevax is a vaccine used to prevent COVID-19 caused by SARS-CoV-2. It is given to adults and children aged 12 years and older. The active substance in Spikevax is mRNA encoding the SARS-CoV-2 Spike protein. The mRNA is embedded in SM-102 lipid nanoparticles.

As Spikevax does not contain the virus, it cannot give you COVID-19.

How the vaccine works
Spikevax stimulates the body's natural defences (immune system). The vaccine works by causing the body to produce protection (antibodies) against the virus that causes COVID-19. Spikevax uses a substance called messenger ribonucleic acid (mRNA) to carry instructions that cells in the body can use to make the spike protein that is also on the virus. The cells then make antibodies against the spike protein to help fight off the virus. This will help to protect you against COVID-19.

2. What you need to know before you are given Spikevax

The vaccine must not be given if you are **allergic** to the active substance or any of the other ingredients of this vaccine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Spikevax if:

- you have previously had a severe, life-threatening **allergic** reaction after any other vaccine injection or after you were given Spikevax in the past.
- you have a very weak or compromised immune system
- you have ever fainted following any needle injection.
- you have a bleeding disorder
- you have a high fever or severe infection; however, you can have your vaccination if you have a mild fever or upper airway infection like a cold

- you have any serious illness
- if you have anxiety related to injections

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

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before you are given Spikevax.

As with any vaccine, the 2-dose vaccination course of Spikevax may not fully protect all those who receive it and it is not known how long you will be protected.

Children
Spikevax is not recommended for children aged under 12 years.

Other medicines and Spikevax
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Spikevax may affect the way other medicines work, and other medicines may affect how Spikevax works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, tell your doctor, pharmacist or nurse before being vaccinated.

Driving and using machines
Do not drive or use machines if you are feeling unwell after vaccination. Wait until any effects of the vaccine have worn off before you drive or use machines.

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

3. How you will be given Spikevax

Spikevax will be given to you as two 0.5 mL injections. It is recommended to administer the second dose of the same vaccine 28 days after the first dose to complete the vaccination course.

Your doctor, pharmacist or nurse will inject the vaccine into a muscle (intramuscular injection) in your upper arm.

After each injection of the vaccine, your doctor, pharmacist or nurse will watch over you for around **15 minutes** to monitor for signs of an allergic reaction.

If you miss an appointment for your 2nd dose of Spikevax
- If you miss an appointment, arrange another visit as soon as possible with your doctor, pharmacist or nurse.
- If you miss a scheduled injection, you may not be fully protected against COVID-19.

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

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Get **urgent** medical attention if you get any of the following signs and symptoms of an allergic reaction:
- feeling faint or light-headed;
- changes in your heartbeat;
- shortness of breath;
- wheezing;
- swelling of your lips, face, or throat;
- hives or rash;
- nausea or vomiting;
- stomach pain.

Talk to your doctor or nurse if you develop any other side effects. These can include:

Very common (may affect more than 1 in 10 people):
- swelling/tenderness in the underarm
- headache
- nausea
- vomiting
- muscle ache, joint aches, and stiffness
- pain or swelling at the injection site
- feeling very tired
- chills
- fever

Common (may affect up to 1 in 10 people):
- rash
- rash, redness, or hives at the injection site (some of which may occur some time after the injection)

Uncommon (may affect up to 1 in 100 people):
- itchiness at the injection site

Rare (may affect up to 1 in 1000 people)
- temporary one-sided facial drooping (Bell's palsy)
- swelling of the face (swelling of the face may occur in patients who have had facial cosmetic injections.)
- dizziness
- decreased sense of touch or sensation

Frequency unknown
- severe allergic reactions with breathing difficulties (anaphylaxis)
- reaction of increased sensitivity or intolerance by the immune system (hypersensitivity)
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this vaccine.

5. How to store Spikevax

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

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

Information about storage, expiry, and use and handling are described in the section intended for healthcare professionals at the end of the package leaflet.

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

6. Contents of the pack and other information

What Spikevax contains

- This is a multidose vial which contains 10 doses of 0.5 mL.
- One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).
- 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 other ingredients are lipid SM-102 (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG), trometamol, trometamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose, water for injections.

What Spikevax looks like and contents of the pack
Spikevax is a white to off white dispersion supplied in a glass vial with a rubber stopper and aluminium seal.

Pack size: 10 multidose vials

Marketing Authorisation Holder:
MODERNA BIOTECH SPAIN, S.L.
Calle Monte Esquinza 30
28010 Madrid
Spain

Manufacturer:
Rovi Pharma Industrial Services, S.A.
Paseo de Europa, 50
28703. San Sebastián de los Reyes
Madrid, Spain

Recipharm Monts
18 Rue de Montbazon
Monts, France 37260

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

België/Belgique/Belgien
Tél/Tel: 3280038405

Lietuva
Tel: (8 5) 214 1995

България
Тел: 008002100471

Česká republika
Tel: 800050719

Danmark
Tlf: 80 83 01 53

Deutschland
Tel: 08001009632

Eesti
Tel: 8000032166

Ελλάδα
Τηλ: 21 1 199 3571

España
Tel: 900031015

France
Tél: 0805543016

Hrvatska
Tel: 08009614

Ireland
Tel: 3531800851200

Ísland
Sími: 8004382

Italia
Tel: +39 800141758

Κύπρος
Τηλ: 35780077065

Latvija
Tel: 37180005882

Luxembourg/Luxemburg
Tél/Tel: 35280026532

Magyarország
Tel: 3680088442

Malta
Tel: 80062397

Nederland
Tel: 08004090001

Norge
Tlf: 4780031401

Österreich
Tel: 43800232927

Polska
Tel: 008003211487

Portugal
Tel: 800210256

România
Tel: 40800630047

Slovenija
Tel: 080488802

Slovenská republika
Tel: 421800105207

Suomi/Finland
Puh/Tel: 358800413854

Sverige
Tel: 020127022

United Kingdom (Northern Ireland)
Tel: 08000857562

This leaflet was last revised in {DD month YYYY}.

This vaccine has been given ‘conditional approval’. This means that there is more evidence to come about this vaccine.

The European Medicines Agency will review new information on this vaccine at least every year and this leaflet will be updated as necessary.

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

Or visit the URL https://www.ModernaCovid19Global.com

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

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

The following information is intended for healthcare professionals only:

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.

Spikevax should be administered by a trained healthcare professional.

The vaccine comes ready to use once thawed.

Do not shake or dilute.

Spikevax vials are multidose. Ten (10) doses can be withdrawn from each multidose vial. Pierce the stopper preferably at a different site each time.

An additional overfill is included in each vial to ensure that 10 doses of 0.5 mL can be delivered.

Thawed vials and filled syringes can be handled in room light conditions.

Spikevax should be administered as two 0.5 mL doses. It is recommended to administer the second dose 28 days after the first dose.

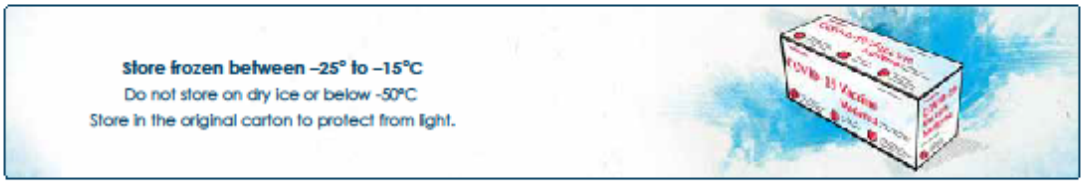
As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following the administration of Spikevax.
Individuals should be observed by a healthcare professional for at least 15 minutes after vaccination.

There are no data to assess the concomitant administration of Spikevax with other vaccines. Spikevax must not be mixed with other vaccines or medicinal products in the same syringe.

The vaccine must be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm. Do not administer this vaccine intravascularly, subcutaneously or intradermally.

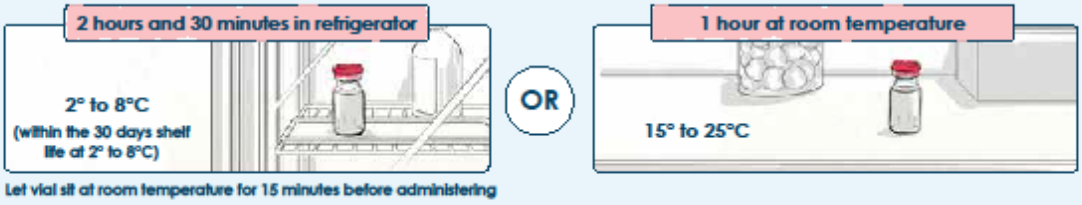
Information about storage and handling

Frozen Storage



Thaw Each Vial Before Use

Vial images for illustrative purposes only



Let vial sit at room temperature for 15 minutes before administering

Instructions Once Thawed

Withdraw each 0.5 mL dose of vaccine from the vial using a new sterile needle and syringe for each injection to prevent transmission of infectious agents from one person to another. **The dose in the syringe should be used immediately.**

Once the vial has been punctured to withdraw the initial dose, the vaccine should be used immediately and be discarded after 19 hours.

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

NEVER refreeze thawed vaccine

Administration

Swirl vial gently after thawing and before each withdrawal.
The vaccine comes ready to use once thawed. **Do not shake or dilute.**