PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

For

Spikevax (elasomeran)

Marketing Authorization Number 68267, 69010

and

Spikevax Bivalent Original / Omicron

(elasomeran / imelasomeran)

Marketing Authorisation Number 69009, 69123

and

Spikevax Bivalent Original / Omicron BA.4-5

(elasomeran / davesomeran)

Marketing Authorization Number 69189, 69211

Dispersion for injection

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Table of Contents

List of Tables

List of Abbreviations

Acronym	Definition
2019-nCoV	2019 novel coronavirus
Ab	antibody
AESI	adverse event of special interest
AR	adverse reaction
COVID-19	disease caused by the novel 2019 coronavirus
CoV	coronaviruses
EMA	European Medicine Agency
EPAR	European Public Assessment Report
EU/EEA	European Union/European Economic Area
Ig	immunoglobulin
mRNA	messenger ribonucleic acid
PL	patient leaflet
RMP	risk management plan
SARS	severe acute respiratory syndrome
SCRI	self-controlled risk interval
SmPC	Summary of Product Characteristics
VAED	vaccine associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease

Overview

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Spikevax Bivalent Original / Omicron is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Spikevax, Spikevax Bivalent Original / Omicron, and Spikevax Bivalent Original / Omicron BA.4-5 in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Moderna Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Spikevax, Spikevax Bivalent Original / Omicron, and Spikevax Bivalent Original / Omicron BA.4-5.

Summary of risk management plan for Spikevax (Elasomeran), Spikevax bivalent Original/Omicron BA.1 (Elasomeran/Imelasomeran), and Spikevax bivalent Original/Omicron BA.4-5 (Elasomeran/Davesomeran)

This is a summary of the risk management plan (RMP) for Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5. The RMP details important risks of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5, how these risks can be minimised, and how more information will be obtained about Spikevax's, Spikevax bivalent Original/Omicron BA.1's, and Spikevax bivalent Original/Omicron BA.4-5's risks and uncertainties (missing information).

Spikevax's, Spikevax bivalent Original/Omicron BA.1's, and Spikevax bivalent Original/Omicron BA.4-5's summaries of product characteristics (SmPCs) and their package leaflets give essential information to healthcare professionals and patients on how Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 should be used.

This summary of the RMP for Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Spikevax's, Spikevax bivalent Original/Omicron BA.1's, and Spikevax bivalent Original/Omicron BA.4-5's RMP.

I The Medicine and What it is Used for

Spikevax is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. Spikevax bivalent Original/Omicron BA.1 is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19. Spikevax bivalent Original/Omicron BA.4-5 is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 6 months of age and older.

The active substance in Spikevax is mRNA encoding the SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and it is given by intramuscular route. The active substances in Spikevax bivalent Original/Omicron BA.1 are mRNA encoding the original SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and mRNA encoding the SARS-CoV-2 Spike protein of the Omicron variant embedded in lipid nanoparticles (imelasomeran) and it is given by intramuscular route. The active substances in Spikevax bivalent Original/Omicron BA.4-5 are mRNA encoding the original SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and mRNA encoding the SARS-CoV-2 Spike protein of the Omicron variant embedded in lipid nanoparticles (davesomeran) and it is given by intramuscular route.

Further information about the evaluation of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 benefits can be found in the Spikevax EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

www.ema.europa.eu/en/medicines/human/EPAR/spikevax

II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5, together with measures to minimise such risks and the proposed studies for learning more about Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about Adverse Reactions (ARs) is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 is not yet available, it is listed under "missing information" below.

In the case of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5, these measures are supplemented with additional pharmacovigilance activities mentioned under the relevant important risks below.

II.A List of Important Risks and Missing Information

Important risks of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Myocarditis Pericarditis
Important potential risks	None
Missing information	Use in pregnancy and while breast-feeding Long-term safety

II.B Summary of Important Risks

Table 2: Important Identified Risk: Myocarditis

Important Identified Risk: Myocarditis	
Evidence for linking the risk to the medicine	Data to evaluate the safety concern were derived from clinical trials and the post-authorisation safety.
Risk factors and risk groups	Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The annual prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men. Patients are usually between the ages of 20 and 50. Acute myocarditis and hyperthyroidism are also common diseases that often present in young, otherwise healthy patients. The spontaneous reports included in the global safety database included 4 cases that reported previous COVID-19 infection (5.9%) with these reports in the 18 to 39 years of age group. There were 5 reports of previous Myocarditis/ Pericarditis medical history (5.9%), 14 reports of cardiovascular conditions (16.5%), 5 with Thyroid conditions (5.9%), and 12 (14.1%) had previous medical histories of allergy-type conditions including history of anaphylaxis.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects 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. (SmPC Section 4.4). 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. (PL Section 2). <u>Additional risk minimisation measures:</u> None

Important Identified Risk: Myocarditis	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P910 Study mRNA-1273-P911 Study mRNA-1273-P301 Study mRNA-1273-P304 Study mRNA-1273-P203 Study mRNA-1273-P306 Study mRNA-1273-P920 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 3: Important Identified Risk: Pericarditis

Important Identified Risk: Pericarditis	
Evidence for linking the risk to the medicine	Data to evaluate the safety concern were derived from the clinical trials and post-authorisation safety data.
Risk factors and risk groups	In most cases, the cause of pericarditis is idiopathic or is assumed to be due to a viral infection. There are several less common infectious and non-infectious causes of pericarditis, but most patients with acute pericarditis present with a history suggestive of recent or concurrent viral illness. Most cases resolve with no long-term sequelae. While pericardial effusions might develop as a result of pericarditis, they are usually minor and rarely result in cardiac tamponade. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65. Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.

Important Identified Risk: Pericarditis	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects 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. (SmPC Section 4.4). 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. (PL Section 2). Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P301 Study mRNA-1273-P304 Study mRNA-1273-P203 Study mRNA-1273-P910 Study mRNA-1273-P306 Study mRNA-1273-P920 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 4 Missing information: Use in Pregnancy and While Breast-Feeding

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P905 Study mRNA-1273-P919 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 5 Long-Term Safety

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P301 Study mRNA-1273-P203 Study mRNA-1273-P205 Study mRNA-1273-P306 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of Spikevax, Spikevax bivalent Original/Omicron BA.1, or Spikevax bivalent Original/Omicron BA.4-5.

II.C.2 Other Studies in Post-Authorisation Development Plan

The following studies are considered ongoing and/or planned additional pharmacovigilance activities:

Table 6 Studies in Post-Authorisation Development Plan

Study Title and Number	Purpose of the Study
Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older (mRNA-1273-P301)	Long-term safety data and durability of vaccine effectiveness (VE).
A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age (mRNA-1273-P203)	Evaluate the safety, reactogenicity, and effectiveness of Spikevax. Assess safety and immunogenicity of mRNA-1273.222.
Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age (mRNA-1273-P204)	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of elasomeran administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age
Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants (mRNA-1273-P205)	Evaluate the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS CoV-2 variants including mRNA-1273.211, Spikevax, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA-1273.222 (Spikevax bivalent Original/Omicron BA.4-5)
A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls (mRNA-1273-P304)	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of SARS-CoV-2 elasomeran vaccine. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.
Post-Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity (mRNA-1273-P903)	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other

Study Title and Number	Purpose of the Study
	outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria.
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (mRNA-1273-P904)	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax?
Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries (mRNA-1273-P905)	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax?
Real-world study of the effectiveness of the Moderna COVID-19 vaccine (mRNA-1273-P901)	Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) in a large integrated healthcare system in the United States.
Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2 (mRNA-1273-P910)	Describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.
Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) (mRNA-1273-P911)	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasomeran (SPIKEVAX) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).
An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy (mRNA-1273-P919)	This observational post-marketing safety study will evaluate the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to Spikevax during pregnancy
Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States (mRNA-1273-P920)	The overarching aim of this study is to characterize the safety of the Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine as used in routine clinical practice.
An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years (mRNA-1273-P306)	Evaluate the safety and reactogenicity of 25 µg of the mRNA-1273.214 vaccine administered as 2-dose primary series 28 days apart in participants aged 6 months to < 6 years. Evaluate the safety and reactogenicity of 10 µg of the mRNA-1273.214 vaccine administered as a single booster dose (BD) at least 4 months post-Dose 2 in participants aged 6 months to < 6 years, who have previously received mRNA-1273 as a primary series