The interim authorisation for the Spikevax bivalent Original / Omicron emergency therapeutic product by the Health Sciences Authority (HSA) of Singapore is made under Regulations 60A(4) and (5)(b) of the Health Product (Therapeutic Products) Regulations, for use and supply as directed by the Government of Singapore.

For additional information about Interim Authorisation, visit HSA at:
https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/psar-emergency-therapeutic-product.

1. NAME OF THE MEDICINAL PRODUCT

Spikevax bivalent Original / Omicron 0.1 mg/mL dispersion for injection
elasomeran / imelasomeran
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Table 1. Qualitative and quantitative composition by strength and type of container

Strength	Container	Dose(s)	Composition
0.1 mg/mL			
	Multidose vial (blue flip-off cap)	5 doses of 0.5 mL each	One dose (0.5 mL) contains 25 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles), and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

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

Imelasomeran contains mRNA, 5'-capped, encoding a full-length, codon-optimised pre-fusion stabilised conformation variant (K983P and V984P) of the SARSCoV-2 spike (S) glycoprotein (Omicron variant, B.1.1.529).

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 bivalent Original / Omicron is indicated for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 in individuals 18 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

Refer to Table 2 for dosing.

Table 2. Spikevax bivalent Original / Omicron posology for booster doses

Strength	Vaccination type	Age(s)	Dose	Recommendations
0.1 mg/mL	Booster dose	Individuals 18 years of age and older	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA	Spikevax bivalent Original / Omicron may be used to boost individuals 18 years of age and older who have received a primary series with Spikevax or a primary series comprised of another COVID-19 vaccine (see section 5.2).

Paediatric population
The safety and efficacy of Spikevax bivalent Original / Omicron in children less than 18 years of age have not yetbeen 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 in individuals who have received Spikevax. 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 30 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

There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax. These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often after the second dose, and more often in younger males.

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Available short-term follow-up data suggest that the symptoms resolve in most individuals, but information on long-term sequelae is lacking.

The increased risk of myocarditis after vaccination with Spikevax is highest in younger males.

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Spikevax. One study showed that in a period of 7 days after the second dose, there were about 1.316 (95% CI 1.299 – 1.333) extra cases of myocarditis in 12 to 29 year-old males per 10,000 compared to unexposed persons. In another study, in a period of 28 days after the second dose, there were 1.88 (95% CI 0.956 – 2.804) extra cases of myocarditis in 16 to 24 year-old males per 10,000 compared to unexposed persons.

Vaccine recipients should be advised to avoid strenuous physical activity for two weeks after vaccination. They should be advised to seek medical attention promptly if they develop chest pain, shortness of breath or abnormal heartbeats.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised.

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.

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 and safety of the vaccine has not been assessed in immunocompromised individuals,

including those receiving immunosuppressant therapy. The efficacy of Spikevax may be lower in immunocompromised individuals.

Based on limited serological evidence with patients who are immunocompromised after solid organ transplantation, a third dose (0.5 mL, 100 mcg) may be considered as part of the primary series in accordance with official recommendations.

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), 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 bivalent Original / Omicron with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with Spikevax during the second and third trimester has not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. 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).

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to Spikevax is negligible. Observational data from women who were breastfeeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants.

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 bivalent Original / Omicron has no or negligible influence on the ability to drive and use machines. However, some ofthe 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 trial 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.

Tabulated list of adverse reactions

The safety profile presented below is based on data generated in a placebo-controlled clinical study on 30,351 adults ≥ 18 years of age.

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 3).

Table 3. Adverse reactions from Spikevax clinical trials and post authorisation experience in individuals 18 years of age and older

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
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/ Paraesthesia
Cardiac disorders	Very rare	Myocarditis Pericarditis
Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Acute and delayed

		urticaria***
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 Injection site erythema
	Common	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.
**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.
*** Includes both acute and delayed urticaria; the frequency category was rare.
****Delayed injection site reactions included pain, erythema and swelling.
*****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 on Day 1 and Day 3, respectively, relative to day of 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.

Participants 18 years of age and older (booster dose)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax are evaluated in an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL, 100 micrograms 1 month apart) of the Spikevax vaccine primary series. In an open-label phase of this study, 167 of those participants received a single booster dose (0.25 mL, 50 micrograms) at least 6 months after receiving the second dose of the primary series. The solicited adverse reaction profile for the booster dose (0.25 mL, 50 micrograms) was similar to that after the second dose in the primary series.

Spikevax bivalent Original / Omicron (booster dose)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax bivalent Original / Omicron are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the Spikevax bivalent Original / Omicron 50 microgram booster dose, and 377 participants received the Spikevax original 50 microgram booster dose.

Spikevax bivalent Original / Omicron had a reactogenicity profile similar to that of the Spikevax original booster given as a second booster dose. The frequency of adverse reactions after immunisation with Spikevax bivalent Original / Omicron was also similar or lower relative to that of a first booster dose of Spikevax original (50 micrograms) and relative to the second dose of the Spikevax primary series (100 micrograms). No new safety signals were identified.

Adverse Event Reporting to HSA

Healthcare professionals are required to report any suspected serious adverse events observed with the use of Spikevax to HSA as soon as possible. All fatal and life-threatening events are to be reported as soon as possible, within 24 hours. Please report the adverse events to the Vigilance and Compliance Branch at Tel: 6866 1111 or report online at https://www.hsa.gov.sg/adverse-events.

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 (elasomeran) and Spikevax bivalent Original / Omicron (elasomeran / imelasomeran) both contain 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.

5.2 Clinical studies

Clinical efficacy

The randomised, placebo-controlled, observer-blind Phase 3 clinical study (NCT04470427) 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). 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 4.

Table 4. 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 interimanalysis 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 88.6, 96.5%).

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.

Additional efficacy analyses

Subgroup analyses of vaccine efficacy 14 days after Dose 2 can be found in Table 5.

Table 5. Subgroup analyses of vaccine efficacy - COVID-19 14 days after Dose 2 per adjudication committee assessments (primary efficacy analysis set) – per-protocol set

Subgroup	Spikevax			Placebo			% Vaccine efficacy (95% CI)**
	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	
Overall At risk*	3,206	4	5.227	3,167	43	57.202	90.9 (74.7, 96.7)
At risk 18 to <65	2,155	2	3.947	2,118	35	70.716	94.4 (76.9, 98.7)
Not At risk 18 to <65	8,396	5	2.594	8,403	121	63.054	95.9 (90.0,98.3)

Females	6,768	7	4.364	6,611	98	62.870	93.1 (85.2,96.8)
Males	7,366	4	2.352	7,462	87	50.730	95.4 (87.4,98.3)

* Participants at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease or HIV infection), regardless of age
** VE and 95% CI from the stratified Cox proportional hazard model

Immunogenicity in participants 18 years of age and older – after booster dose (0.25 mL, 50 micrograms)

The safety, reactogenicity, and immunogenicity of a booster dose of Spikevax are evaluated in an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL, 100 micrograms 1 month apart) of the Spikevax vaccine as primary series. In an open-label phase, 149 of those participants (Per-Protocol Set) received a single booster dose (0.25 mL, 50 micrograms) at least 6 months after receiving the second dose in the primary series. A single booster dose (0.25 mL, 50 micrograms) was shown to result in a geometric mean fold rise (GMFR) of 12.99 (95% CI: 11.04, 15.29) in neutralising antibodies from pre-booster compared to 28 days after the booster dose. The GMFR in neutralising antibodies was 1.53 (95% CI: 1.32, 1.77) when compared 28 days post dose 2 (primary series) to 28 days after the booster dose.

Immunogenicity in participants 18 years of age and older – after Spikevax bivalent Original / Omicron booster dose (0.5 mL, 50 micrograms)

The safety, reactogenicity, and immunogenicity of a Spikevax bivalent Original / Omicron booster dose are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the Spikevax bivalent Original / Omicron 50 microgram booster dose, and 377 participants received the Spikevax original 50 microgram booster dose.

Study P205 Part G evaluated the safety, reactogenicity and immunogenicity of Spikevax bivalent Original / Omicron when administered as a second booster dose to adults who previously received 2 doses of Spikevax (100 microgram) as a primary series and a booster dose of Spikevax original (50 micrograms) at least 3 months prior to enrollment. In P205 Part F, study participants received Spikevax bivalent Original / Omicron (50 micrograms) as a second booster dose and the Part F group serves as a within-study, non-contemporaneous comparator group to the Spikevax bivalent group.

In this study, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). In the primary analysis, the original SARS-CoV-2 estimated neutralising antibody geometric mean titre (GMT) and corresponding 95% CI was 6422.3 (5990.1, 6885.7) and 5286.6 (4887.1, 5718.9) 28 days after the Spikevax bivalent and Spikevax original booster doses, respectively. This GMT represents the ratio between response of Spikevax bivalent versus Spikevax original against the ancestral SARS-COV-2 (D614G) strain. The GMR (97.5% CI) was 1.22 (1.08, 1.37) meeting the pre-specified criterion for non-inferiority (lower bound of 97.5% CI $\geq$0.67).

The estimated Day 29 neutralising antibody GMTs against Omicron were 2479.9 (2264.5, 2715.8) and 1421.2 (1283.0, 1574.4) in the Spikevax bivalent and Spikevax original booster groups, respectively, and the GMR (97.5% CI) was 1.75 (1.49, 2.04), which met the pre-specified superiority criterion (lower bound of CI >1).

Observed neutralising antibody titres for Omicron subvariants BA.4/BA.5 after the Spikevax bivalent Original / Omicron booster dose
Participants who received Spikevax bivalent Original / Omicron as a second booster dose against the Omicron BA.4/BA.5 subvariant had the following results in the PPSI*, PPSI – Neg†, and PPSI – Pos‡ populations:

- The pre-booster GMT (95% CI) against Omicron BA.4/BA.5 subvariant was 172.7 (147.5-202.3) which increased to 940.6 (826.3-1070.6) 28 days after the booster vaccine was administered

resulting in a GMFR (95% CI) of 5.4 (5.0-5.9) for participants in the PPSI population (regardless of SARs-CoV-2 infection status at pre-booster baseline).

- The pre-booster GMT (95% CI) against Omicron BA.4/BA.5 subvariant was 115.6 (98.5-135.6) which increased to 727.4 (632.9-836.1) 28 days after the booster vaccine was administered resulting in a GMFR (95% CI) of 6.3 (5.7-6.9) for participants in PPSI – Neg population.
- The pre-booster GMT (95% CI) against Omicron BA.4/BA.5 subvariant was 719.5 (531.6-973.9) which increased to 2337.4 (1825.5-2992.9) 28 days after the booster vaccine was administered resulting in a GMFR (95% CI) of 3.3 (2.8-3.8) for participants in PPSI – Pos population.

*PPSI = Per-protocol set for immunogenicity.

†PPSI – Neg = Per-protocol Set for immunogenicity – SARs-CoV-2 Negative at baseline.

‡PPSI – Pos = Per-protocol Set for immunogenicity – SARs-CoV-2 Positive at baseline.

These results indicate that Spikevax bivalent Original / Omicron booster antibody levels are comparable to those obtained in the Phase 3 study for which efficacy was demonstrated.

Elderly population

Spikevax was assessed in individuals 18 years of age and older, including 3,768 subjects 65 years of age and older. The efficacy of Spikevax in elderly (≥65 years) was 86.4% (95% confidence interval 61.4%, 95.2%). In a subset of these vaccinated elderly subjects with comorbidities (n=1051), efficacy was 75.2% (95% confidence interval -16.9%, 94.7%).

Paediatric population

Interim Authorisation of Spikevax bivalent Original / Omicron does not include use in individuals younger than 18 years of age.

5.3 Pharmacokinetic properties

Not applicable.

5.4 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 multidose vial (0.1 mg/mL)

9 months at -50ºC to -15ºC.

After removal from the freezer, the unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30days. Within this period, up to 12 hours may be used for transportation at 2°C to 8°C (see section 6.4).

Chemical and physical stability has also been demonstrated for unopened vaccine vials when stored for 12 months at -50°C to -15°C **provided that once thawed and stored at 2°C to 8°C,** protected from light, **the unopened vial will be used up within a maximum of 14 days** (instead of 30 days, when stored at -50ºC to -15ºC for 9 months).

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 multidose vial (0.1 mg/mL)

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 -50ºC to -15ºC.
Store in the original carton to protect from light.
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 in appropriate qualified insulated shippers (within the 30 days shelf life at 2°C to 8°C). Protect from mechanical stress during transport.

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

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

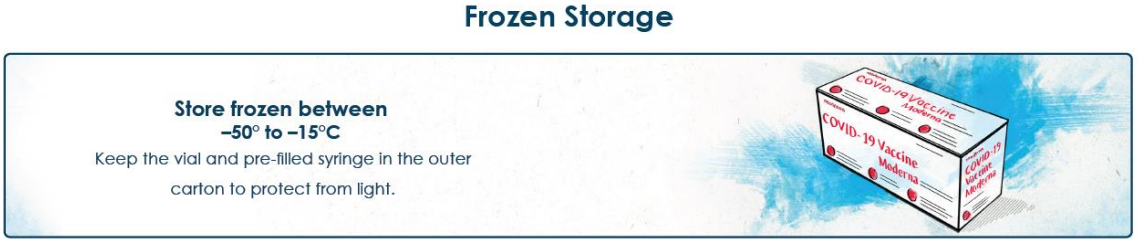
Each vial contains 2.5 mL.

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.

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



The vaccine comes ready to use once thawed.

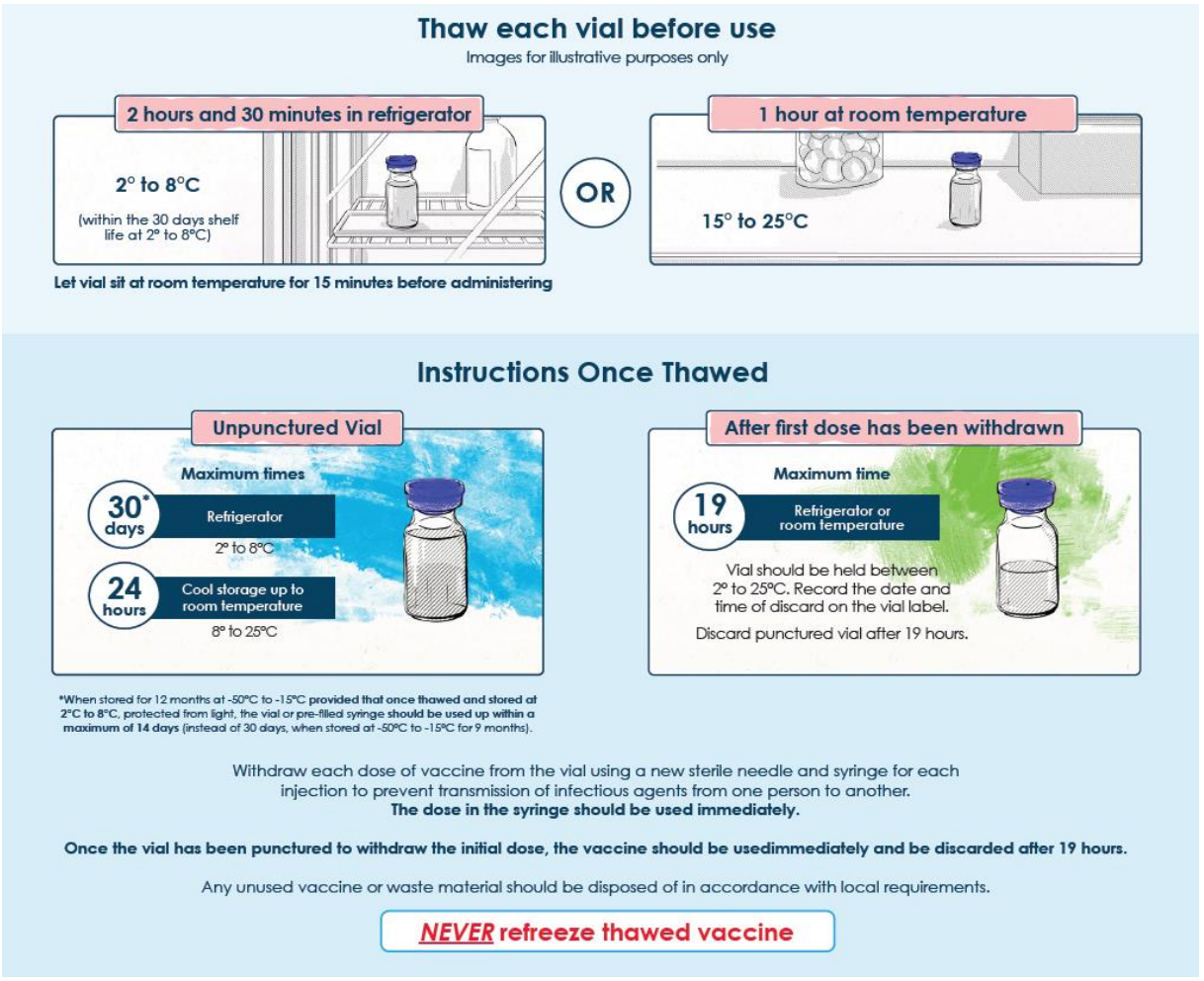
Do not shake or dilute. Swirl the vial gently after thawing and before each withdrawal.

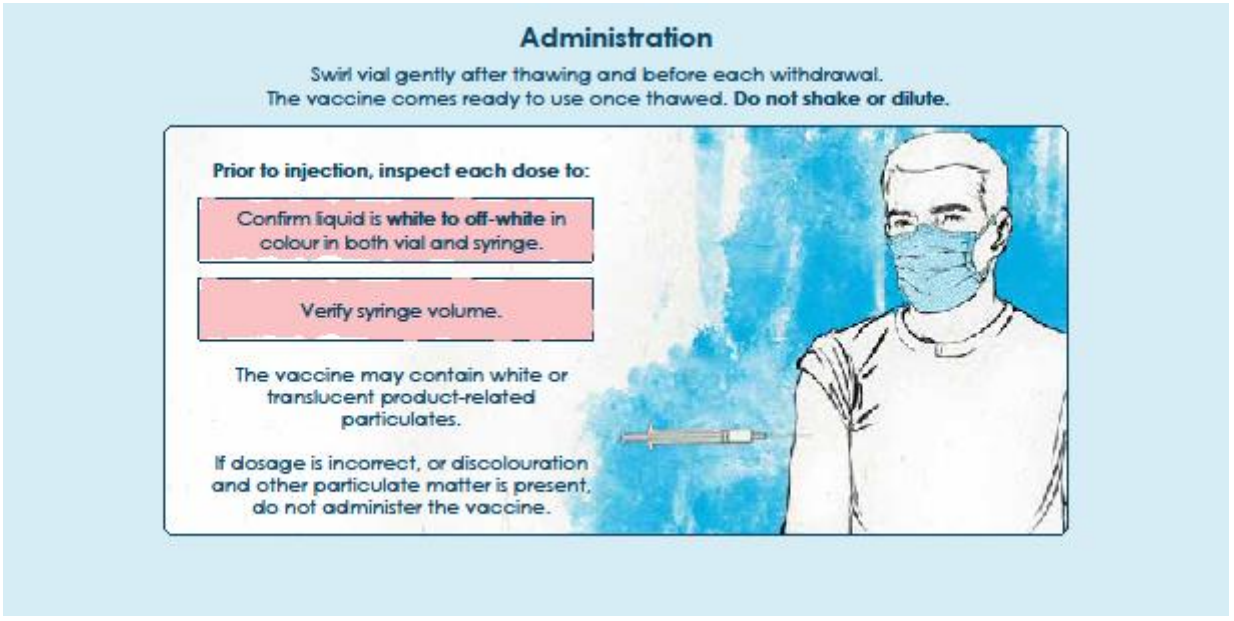
Spikevax vials are multidose.

Five (5) doses (of 0.5 mL each) can be withdrawn from each vial (blue flip-off cap).

Pierce the stopper preferably at a different site each time.

An additional overfill is included in each vial to ensure that 5 doses of 0.5 mL can be delivered.





7. PRODUCT OWNER

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8. DATE OF TEXT

October 2022