The interim authorisation for the COVID-19 Vaccine Moderna 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

COVID-19 Vaccine Moderna 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

COVID-19 Vaccine Moderna 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

Individuals 18 years of age and older
COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of COVID-19 Vaccine Moderna should receive the second dose of COVID-19 Vaccine Moderna to complete the vaccination course.

Paediatric population

The safety and efficacy of COVID-19 Vaccine Moderna in children and adolescents less than 18 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
Individuals with history of any anaphylaxis should not receive the vaccine.

Anaphylaxis has been reported following the COVID-19 Vaccine Moderna during mass vaccination outside of clinical trials. 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 COVID-19 Vaccine Moderna.

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, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of COVID-19 Vaccine Moderna 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). Available data on COVID-19 Vaccine Moderna administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Breast-feeding

It is unknown whether COVID-19 Vaccine Moderna is excreted in human milk.

Fertility

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

4.7 Effects on ability to drive and use machines

COVID-19 Vaccine Moderna 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
The safety of COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna (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>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
<td>Lymphadenopathy*</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Acute peripheral facial paralysis**</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very common</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arthralgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Injection site pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injection site swelling</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Injection site erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injection site urticaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injection site rash</td>
</tr>
<tr>
<td>Common</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>Facial swelling***</td>
<td>Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site.</td>
</tr>
</tbody>
</table>
*Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna, that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

Adverse Event Reporting to HSA

Healthcare professionals are required to report any suspected serious adverse events observed with the use of COVID-19 Vaccine Moderna 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, Fax: 6478 9069, 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

COVID-19 Vaccine Moderna 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

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 COVID-19 Vaccine Moderna. 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 COVID-19 Vaccine Moderna.

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 COVID-19 Vaccine Moderna (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 2.

Table 2: Vaccine Efficacy Analysis: confirmed COVID-19 regardless of severity starting 14 days after the 2nd dose – Per-Protocol Set

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>COVID-19 Vaccine Moderna</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects N</td>
<td>COVID-19 Cases n</td>
</tr>
<tr>
<td>Overall (≥18)</td>
<td>14,134</td>
<td>11</td>
</tr>
<tr>
<td>18 to &lt;65</td>
<td>10,551</td>
<td>7</td>
</tr>
<tr>
<td>≥65</td>
<td>3,583</td>
<td>4</td>
</tr>
<tr>
<td>≥65 to &lt;75</td>
<td>2,953</td>
<td>4</td>
</tr>
<tr>
<td>≥75</td>
<td>630</td>
<td>0</td>
</tr>
</tbody>
</table>

*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

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 COVID-19 Vaccine Moderna 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 86.6, 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.

Elderly population

COVID-19 Vaccine Moderna was assessed in individuals 18 years of age and older, including 3,768 subjects 65 years of age and older. The efficacy of COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna does not include use in individuals younger than 18 years of age.

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 COVID-19 Vaccine Moderna 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 mRNA-1273 vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lipid SM-102
Cholesterol
1,2-distearoyl-sn-glycero-3-phosphocholine (DPC)
1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG)
Tromethamol
Tromethamol 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 -25°C to -15°C.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days.

Once thawed the vaccine should not be re-frozen.

The unopened vaccine may be stored at 8°C to 25°C up to 12 hours after removal from refrigerated conditions.

Punctured Vial:
Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 25°C after initial puncture. 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 in a freezer frozen between -25°C to -15°C.
Store in the original carton to protect from light.
Do not store on dry ice or below -40°C.
For storage conditions after thawing and first opening see section 6.3.

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 0.5mL.

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.

COVID-19 Vaccine Moderna vials are multidose.

Ten (10) doses (of 0.5mL each) can be withdrawn from each vial.

An additional overfill is included in each vial to ensure that 10 doses of 0.5 mL can be delivered.
Thaw Each Vial Before Use
Vial images for illustrative purposes only

- **2 hours and 30 minutes in refrigerator**
  - 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**
  - **30 days**
    - Refrigerator: 2° to 8°C
  - **12 hours**
    - Cool storage up to room temperature: 18° to 25°C

- **After first dose has been withdrawn**
  - **Maximum time**
    - **6 hours**
      - Refrigerator or room temperature

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 6-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 color 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 discoloration and other particulate matter is present, do not administer the vaccine.

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7. PRODUCT OWNER

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