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Dear Healthcare Professional

INTERIM AUTHORISATION OF MODERNA COVID-19 VACCINE FOR ACTIVE IMMUNISATION TO PREVENT COVID-19 DISEASE IN SINGAPORE

The Health Sciences Authority (HSA), in consultation with its Medicines Advisory Committee and Panel of Infectious Diseases Experts, would like to inform healthcare professionals on the interim authorisation of Moderna COVID-19 Vaccine for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 18 years of age and over.

Interim Authorisation via Pandemic Special Access Route (PSAR)

2 HSA has granted an interim authorisation under the Pandemic Special Access Route[1] (PSAR) for Moderna COVID-19 Vaccine. This is the second COVID-19 vaccine to be granted interim authorisation under PSAR.[2] This regulatory pathway facilitates access to critical novel vaccines, medicines and medical devices during a pandemic such as the current COVID-19 pandemic.

3 Moderna COVID-19 Vaccine is a chemically synthesised single-stranded, 5'-capped messenger RNA (mRNA), encoding the viral spike (S) protein of SARS-CoV-2. It is supplied in ready-to-use multidose vials (10 doses/vial). The vaccine is to be administered intramuscularly as a series of two 100 µg doses (0.5 mL each) 28 days apart.

4 HSA's interim authorisation is based on the totality of evidence from the quality, non-clinical and clinical data available to date. There was adequate chemistry and manufacturing controls data demonstrating that the vaccine's quality met the required standards, as well as non-clinical data suggesting robust immune response, Th1-biased cellular response[3], and favourable toxicology profile in animals. These, taken together with the immunogenicity data in the early Phase studies, as well as the high vaccine efficacy shown in the Phase III study and the safety data available to date, were assessed by HSA that the benefit outweighs the known risk of the use of the vaccine. HSA will continually review the regulatory recommendation as data from on-going clinical and manufacturing studies become available. The company will be required to submit these data to HSA to ensure the continued efficacy and safety of the vaccine.

Scientific Considerations for Efficacy and Safety

Efficacy

5 The efficacy of Moderna COVID-19 Vaccine is based on clinical data in subjects aged 18 to 95 from the Phase III COVE study. A total of 30,351 subjects were randomised in 1:1 ratio to receive either the vaccine or placebo, administered by intramuscular injection in two 100 µg doses 28 days apart (window allowance for Dose 2: Day 26 to Day 36). The proportion

[1] https://www.hsa.gov.sg/hsa-psar
[2] The Pfizer-BioNTech Vaccine was the first COVID-19 vaccine to be authorised for use in Singapore under PSAR and requires two doses of vaccine to be administered 21 days apart, in individuals aged 16 years and above.
[3] T helper type 1 (Th1) cells secrete cytokines such as interferon-gamma, IL-2, which activate other immune cells that may play a protective role against severe lung disease.

of subjects in different age groups is shown in Table 1. The study also included about 22% of subjects with at least one comorbidity that increases the risk of severe COVID-19 disease, e.g. diabetes, chronic lung disease, cardiac disease, severe obesity, liver disease and virologically suppressed human immunodeficiency virus (HIV) infection.

Table 1: Breakdown of age groups of subjects in COVE study

Age group	Proportion of subjects
18 to < 65	75.2%
≥ 65	24.8%
≥ 75	4.3%

6 The results available to date (Table 2) showed that the vaccine, when given as two-dose regimen 28 days apart, achieved 94.1% (95% CI: 89.3%, 96.8%) efficacy for the prevention of symptomatic COVID-19 disease as compared with placebo in subjects who were sero-negative at baseline. The number of cases of laboratory confirmed symptomatic COVID-19 disease, based on data collected more than 14 days after completion of vaccination in subjects who were sero-negative at baseline, was 11 and 185 cases in the vaccine and placebo groups respectively. Consistent vaccine efficacy of 93.6% (95% CI: 88.6%, 96.5%) was also seen in all subjects regardless of baseline sero-status.

Table 2: Breakdown of efficacy results by subgroups of subjects in COVE study

Study Population	Results
Overall vaccine efficacy (VE)[∞]	94.1% (95% CI: 89.3, 96.8)
– VE in subjects ≥ 65 years old (24.8%)	86.4% (95% CI: 61.4, 95.2)
– VE in subjects with comorbidities (22.5%)	90.9% (95% CI: 74.7, 96.7)
– VE in subjects ≥ 65 years old with comorbidities (7.3%)	75.2% (95% CI: -16.9, 94.7)
– VE in Asians (4.3%)	100%
VE against severe COVID-19 disease	100%

[∞] Vaccine efficacy (VE) is the percentage reduction in the incidence of disease in a vaccinated group compared to an unvaccinated group.

7 In the subgroup of older subjects aged ≥ 65 years, the efficacy point estimates were observed to be lower at 86.4% (95% CI: 61.4%, 95.2%), and 75.2% (95% CI: -16.9%, 94.7%) in those with comorbidities. Nonetheless, the protection conferred by the vaccine in this subgroup of population who is known to have higher risk for COVID-19 disease remains clinically meaningful, also taking into account the 100% vaccine efficacy demonstrated against severe disease, where there were no severe cases in the vaccine group and there were 30 severe cases in the placebo group.

8 The number of Asian subjects recruited in the Phase III study was relatively small (approximately 4% of the study population). There were no COVID-19 cases among Asian subjects in the vaccine group and five cases in the placebo group, giving rise to an efficacy point estimate of 100%. The interpretation of the observed efficacy is currently limited by the small number of cases. Longer term follow-up and accrual of more cases would help to re-confirm these observations. At present, there is no evidence of differential efficacy in Asians based on the available data.

9 As the length of follow-up at the data cut-off for efficacy analyses was limited to two months after the second dose of vaccination, a longer duration would be needed to fully assess the duration of protection. Nonetheless, based on the available data, there is no waning of protection at the cut-off date of two months. There is currently insufficient data on the vaccine efficacy against re-infection and asymptomatic infection, and the on-going Phase III study which is planned for 24 months follow-up post-Dose 2 is expected to generate more data to address these issues. There is no clinical data to inform on vaccine-associated risks in pregnant women, in those aged below 18 years and in immunocompromised persons.

Safety

10 The safety analysis comprised data from more than 15,000 subjects who had received at least one dose of the vaccine. The duration of follow-up was more than two months for 61% of subjects and more than one month for 88% of subjects.

11 The most common solicited adverse reactions[4] were injection site reactions, fatigue, headache, muscle pain, joint pain, chills, nausea / vomiting and fever. Overall, the majority of reactogenic adverse reactions were mild or moderate (Grade 1 or 2) in intensity and resolved within a few days after vaccination. The incidences of severe (Grade 3 and 4) reactogenic events were generally low. See Table 3 for the summary of the solicited adverse reactions reported in the vaccine group compared to the placebo group.

Table 3: Comparison of solicited adverse reactions in vaccine and placebo arm

Solicited adverse reactions	**Vaccine (n=15,179)**	**Placebo (n=15,163)**
Injection site pain*		
Overall	92.0%	26.6%
Grade 3	6.1%	0.6%
Lymphadenopathy*		
Overall	19.8%	7.2%
Grade 3	0.7%	0.3%
Injection site swelling**		
Overall	14.7%	0.6%
Grade 3	2.1%	0.1%
Injection site redness**		
Overall	10.0%	0.8%
Grade 3	2.1%	0.2%
Fatigue^		
Overall	70.0%	36.6%
Grade 3	10.1%	1.3%
Grade 4	0.007%	0
Headache*		
Overall	64.7%	37.0%
Grade 3	5.7%	2.2%
Muscle pain^		
Overall	61.5%	20.5%
Grade 3	9.1%	0.6%
Joint pain^		
Overall	46.4%	17.6%
Grade 3	5.3%	0.5%
Grade 4	0.007%	0
Chills^		
Overall	45.4%	9.7%
Grade 3	1.4%	0.2%
Nausea/Vomiting$^{\Delta}$		
Overall	23.0%	11.3%
Grade 3	0.2%	0.2%
Grade 4	0.007%	0
Fever$^{\#}$		
Overall	15.5%	0.6%
Grade 3	1.4%	0.03%
Grade 4	0.1%	0.06%

*Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalisation.
**Grade 3: > 10cm.
^Grade 3: Significant; prevents daily activity; Grade 4: Requires emergency room visit or hospitalisation.
$^{\Delta}$Grade 3 prevents daily activity and requires outpatient intravenous hydration; Grade 4 requires emergency room visit or hospitalisation for hypotensive shock.
$^{\#}$Grade 3: ≥39.0 to ≤40.0°C; Grade 4: >40°C.

[4]Solicited adverse reactions are pre-defined local and systemic adverse reactions which the subjects in the clinical study were asked to look out for and report in an electronic diary using a structured questionnaire for the first 7 days post-vaccination. These adverse reactions are listed in Table 3.

12 Overall, the safety profile of the vaccine is mainly characterised by reactogenic events, which is consistent with what is known for mRNA vaccines. The frequencies of serious adverse events (SAEs) were low, 1.0% of subjects both in vaccine and placebo groups. The length of the median follow-up period of two months after the completion of vaccination is considered reasonably adequate for assessing solicited local and systemic events, as well as potential immune-mediated adverse events, which generally have an onset within six weeks following vaccination.

13 Nonetheless, a longer duration of safety follow-up would allow further characterisation of SAEs and adverse events of special interest (AESIs), including the detection of SAEs as well as the potential risk of enhanced respiratory disease (ERD). The current data does not suggest a signal of potential risk of ERD, in view that there was no evidence of increased disease severity in the Phase III study, and the non-clinical and Phase I studies showed a Th1-biased cellular response.

14 During the Phase III study, three adverse events of Bell's palsy were reported with the vaccine group and one case in the placebo group, all of which were assessed by the investigator as unrelated. While the number of events was low and fell within the background rate, healthcare professionals are advised to pay attention to potential neurological adverse events.

15 The Moderna COVID-19 Vaccine has been authorised for use in other countries such as the United States (US), United Kingdom, the European Union and Canada. Based on a report published by the US Centres for Disease Control and Prevention (CDC)[5], cases of allergic reactions including anaphylaxis have been reported in the US following the administration of the Moderna COVID-19 Vaccine. Of these cases, most of the vaccine recipients had documented history of allergies or allergic reactions and several had previous history of anaphylaxis.

16 Anaphylaxis after vaccination is a known and rare adverse event. HSA advises the following precautionary measures:

- Individuals with history of any anaphylaxis should not receive the vaccine;
- A second dose should not be given to those who have experienced anaphylaxis with the first dose;
- Vaccine recipients should be observed for at least 30 minutes after vaccination for signs of allergic reactions;
- Appropriate medical treatment needed to manage immediate allergic reactions must be immediately available in the event of an acute anaphylactic reaction following the administration of the vaccine.

Adverse Event Monitoring and Reporting

17 Healthcare professionals are advised to remind vaccine recipients to monitor and inform them of any adverse events experienced that may be associated with the vaccine, and also to check with the recipients for any adverse events when they return for their second dose of the vaccine.

18 To facilitate HSA's safety monitoring, and in view of the availability of two vaccines for prevention of COVID-19 disease, healthcare professionals are required to specify the brand name and batch number of the vaccine administered to individuals when submitting the notification on COVID-19 vaccinations to the National Immunisation Registry, as well as when reporting suspected adverse events to HSA.

[5] https://www.cdc.gov/mmwr/volumes/70/wr/mm7004e1.htm?s_cid=mm7004e1_w

19 Healthcare professionals are required to report any suspected SAEs observed with the use of Moderna COVID-19 Vaccine to HSA as soon as possible. **All fatal and life-threatening SAEs/AESIs that happened within the first 30 minutes of observation post-vaccination** (e.g. anaphylaxis) should be reported to HSA **as soon as possible,** once the patient has been managed and **no longer than 3 hours**. All other fatal and life-threatening events are to be reported **as soon as possible, within 24 hours** (note: fatal events are reportable as Coroner's cases under the Coroners Act). All other SAEs and AESIs are to be reported **as soon as possible, within 48 hours.**

20 Please report the adverse events to the Vigilance and Compliance Branch of HSA:

- through the Adverse Drug Reactions/Drug Allergy module of the Critical Medical Information Store (CMIS) available in the Electronic Medical Records (EMR) of public health institutions; or
- online at https://www.hsa.gov.sg/adverse-events

21 HSA will actively monitor the adverse events associated with COVID-19 vaccines in the local population and collaborate with international regulatory counterparts to detect safety signals associated with them. HSA will keep healthcare professionals informed of any significant safety signals associated with COVID-19 vaccines. COVID-19 vaccine information and safety updates will be updated on https://www.hsa.gov.sg/covid-19-information-and-advisories.

22 Should you have further queries regarding the above information, please contact the Therapeutic Products Branch at Tel: 6866 1111 or email: HSA_TP_enquiry@hsa.gov.sg.

Thank you.

Yours faithfully

MS AGNES CHAN
DIRECTOR
THERAPEUTIC PRODUCTS BRANCH
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HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health