REGULATORY UPDATE **No.72**

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Dear Healthcare Professional

INTERIM AUTHORISATION OF PFIZER-BIONTECH COVID-19 VACCINE (BNT162b2) 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 Pfizer-BioNTech COVID-19 Vaccine for active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals 16 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 (PSAR) for Pfizer-BioNTech COVID-19 Vaccine (BNT162b2). This regulatory pathway facilitates access to critical novel vaccines, medicines and medical devices during a pandemic such as the current COVID-19 pandemic. Using PSAR, HSA can start evaluating new vaccines from the early stages of clinical studies, as and when real-time data is submitted by companies on a "rolling", or staggered basis. Companies can continue their clinical trials and development while HSA reviews the submitted data concurrently. To further compress developmental timelines, innovative and adaptive trial designs have also been used to run trials in parallel or to combine different phases of a clinical trial, without compromising the scientific rigour of the clinical trials. Such regulatory agility and flexibility allows for speedier development and evaluation.

3 BNT162b2 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 multidose vials and must be diluted before use. One vial (0.45 mL) contains 5 doses of 30 micrograms of BNT162b2 mRNA (encapsulated in lipid nanoparticles). The vaccine is to be administered intramuscularly after dilution as a series of two doses (0.3mL each) 21 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[1], and favourable toxicology profile in animals. These, taken together with the immunogenicity data in early Phase studies, as well as the high vaccine efficacy shown in the Phase III study and the safety data available to-date, HSA has assessed 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.

[1] 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.

Scientific Considerations for Efficacy and Safety

Efficacy

5 The efficacy of Pfizer-BioNTech COVID-19 Vaccine is based on clinical data in subjects aged 16 to 91 from the Phase III study. See Table 1 below for the breakdown of the different age groups. The study also included about 46% of subjects with one or more comorbidities that increase the risk of severe COVID-19 disease, e.g. diabetes, chronic pulmonary disease, malignancy, myocardial infarction, renal disease, liver disease, congestive heart failure, and obesity.

Table 1. Breakdown of the different age groups.

Age group	Proportion of Subjects
16-55 years old	57.2%
>55-64 years old	20.7%
⩾65 years old	21.9%

6 The results available to-date showed that the vaccine, when given as a 2-dose regimen 21 days apart, achieved 95.0% (95% CI: 90.3% to 97.6%) efficacy against laboratory confirmed symptomatic COVID-19 disease, based on data collected more than 7 days after completion of vaccination in subjects who were sero-negative at baseline, with 8 and 162 cases in the vaccine and placebo groups respectively. Consistent results were also seen in all subjects regardless of baseline sero-status, 94.6% (95% CI: 89.9% to 97.3%). Subgroup analyses showed similar vaccine efficacy of 93% or more across age groups (16-55 years; >55 years; ≥65 years), genders and subjects with medical comorbidities.

7 It was observed that vaccine efficacy after the first dose was lower at 52.4% (95% CI: 29.5%, 68.4%), suggesting that a single dose might not confer adequate protection and two doses are required for optimal protection against COVID-19 disease. Vaccine recipients should be reminded to return in 3 weeks' time for the second dose in order to achieve the necessary protection.

8 Vaccine efficacy against severe COVID-19 disease is currently inconclusive, as there were too few cases in study subjects who completed the 2-dose regimen (1 case in the vaccine group vs 3 cases in the placebo group) to confirm the efficacy point estimate (66.4%; 95% CI: -125.5% to 96.3%). Nonetheless, the overall data from all subjects who received at least one dose suggests a trend of a lower number of severe disease in the vaccine group (1 case in the vaccine group vs 9 cases in the placebo group).

9 The number of Asian subjects recruited in the Phase III study was relatively small (approximately 4% of the study population). The point estimate of efficacy was 74.4% (95% CI: -158.7% to 99.5%) with a wide confidence interval, which could be attributed to the reduced sample size and the very small number of events (1 case in the vaccine group vs 4 cases in the placebo group), and does not allow a precise estimate of vaccine efficacy. Nonetheless, current evidence does not suggest reduced efficacy in Asians. Longer follow-up and accrual of more cases would help provide a more precise estimate of the vaccine efficacy.

10 As the length of follow-up at the data cut-off for efficacy analyses was limited to 2 months after the second dose of vaccination, a longer duration will 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 2 months. There is currently insufficient data on the vaccine efficacy against re-infection and asymptomatic infection, and the on-going Phase III study is expected to generate more data to address these issues. There is also no data in immunocompromised persons and pregnant women. Studies are ongoing for children between the ages of 12 to 15 years. As further data are required, no recommendation can be made at this time for these groups.

Safety

11 The safety analysis comprised data from more than 20,000 patients who had received at least one dose of the vaccine. Duration of follow-up was more than 2 months for approximately 45% of subjects and more than 1 month for approximately 80% of subjects. The most common solicited adverse reactions were injection site reactions, fatigue, headache, muscle pain, chills, joint pain, fever, diarrhoea, and vomiting. Overall, the majority of reactogenic adverse events were mild or moderate (Grade 1 or 2) in intensity and resolved within a few days after vaccination. The incidences of severe (Grade 3)[2] reactogenic events were generally low. See Table 2 below on the summary of the solicited[2] adverse events reported in the vaccine group compared to the placebo group.

Table 2: Comparison of solicited adverse events in vaccine and placebo arm.

Solicited adverse events	**Vaccine**	**Placebo**
Injection site pain		
Overall	84.1%	17.0%
Grade 3	1.4%	0.0%
Fatigue		
Overall	62.9%	35.6%
Grade 3	4.2%	0.6%
Headache		
Overall	55.1%	34.1%
Grade 3	2.4%	1.0%
Muscle pain		
Overall	38.3%	13.4%
Grade 3	1.8%	0.2%
Chills		
Overall	31.9%	7.0%
Grade 3	1.7%	0.1%
Joint pain		
Overall	23.6%	8.8%
Grade 3	0.8%	0.1%
Diarrhoea		
Overall	15.7%	14.0%
Grade 3	0.3%	0.2%
Fever		
Overall	14.2%	0.9%
Grade 3	0.9%	0.2%
Injection site swelling		
Overall	10.5%	1.0%
Grade 3	0.4%	0.1%
Injection site redness		
Overall	9.5%	1.6%
Grade 3	0.7%	0.1%
Vomiting		
Overall	2.0%	1.5%
Grade 3	0.1%	0.0%

12 The observed adverse events were not unexpected for a vaccine. A 2-month duration allows reasonable time for assessing solicited local and systemic events, as well as potential immune-mediated adverse events, which generally have an onset within 6 weeks following vaccination. However, a longer duration of safety follow-up will allow further characterisation of serious adverse events and adverse events of special interest, including the detection of serious adverse events as well as the potential risk of enhanced respiratory disease (ERD). Current data does not suggest a signal of potential risk of ERD, in view that there was no

[2] Solicited adverse events are pre-defined local and systemic adverse events 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 events are listed in Table 2. An adverse event may be classified as Grade 3 (i.e. severe) if it prevents daily routine activity or requires medical intervention.

evidence of increased disease severity in the Phase III study, and the non-clinical and Phase I studies showed a Th1-biased cellular response.

13 During the Phase III study, two related adverse events of Bell's palsy and one related serious adverse event of paraesthesia were reported with the vaccine group. While numbers of events were low and fell within the background rate, healthcare professionals are advised to pay attention to potential neurological adverse events.

14 Given the two reports of anaphylaxis in the UK (the two vaccine recipients had past history of anaphylaxis) following the first roll-out of the vaccine, and that this is the first COVID-19 vaccine in Singapore, 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 to 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 an acute anaphylactic reaction occurs following administration of the vaccine.

Adverse Event Monitoring and Reporting

15 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.

16 To facilitate HSA's safety monitoring, and in anticipation of the availability of other similar 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, as well as when reporting suspected adverse events to HSA.

17 Healthcare professionals are required to report any suspected serious adverse events observed with the use of Pfizer-BioNTech COVID-19 Vaccine 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.

18 HSA will actively monitor the adverse events associated with the vaccine in the local population and collaborate with international regulatory counterparts to detect safety signals associated with the vaccine. HSA will keep healthcare professionals informed of significant safety signals associated with the vaccine.

19 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
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THERAPEUTIC PRODUCTS BRANCH
HEALTH PRODUCTS REGULATION GROUP
HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health