Report on Evaluation of Safety, Efficacy and Quality of CoronaVac COVID-19 Vaccine (Vero Cell) Inactivated

(*Revised on 22 February 2021)*

BACKGROUND

In view of the pandemic of COVID-19, the Government strives to provide sufficient supplies of vaccines for the Hong Kong population as early as possible. To expedite and allow early use of the vaccines, the Government published the Prevention and Control of Disease (Use of Vaccines) Regulation ("the Regulation"), Cap. 599K, Laws of Hong Kong, in the Gazette on 23 December 2020. The Regulation provides the legal framework under the present state of public health emergency to bring in COVID-19 vaccines which satisfy the criteria of safety, efficacy and quality for emergency use in Hong Kong.

2. The Regulation empowers the Secretary for Food and Health to authorize and allow the specified use of a COVID-19 vaccine in Hong Kong under the emergency situation, which is basically for vaccination programmes conducted by the Government, having regard to the submitted clinical data of the COVID-19 vaccine (including Phase 3 clinical research data), the expert advice of an independent advisory panel and the approval given by a regulatory authority in a place outside Hong Kong that performs the function of approving pharmaceutical products (including emergency use).

3. The Advisory Panel on COVID-19 Vaccines ("the Advisory Panel"), as appointed by the Chief Executive, was established to provide assessment and expert advice to the Secretary for Food and Health in relation to the safety, efficacy, and quality of a COVID-19 vaccine under application for authorization under the Regulation. The Advisory Panel is also responsible for advising the Secretary for Food and Health on the conditions to be attached to an authorization and revocation of an authorization.

APPLICATION FOR AUTHROIZATION

4. On 25 January 2021, an application for authorization under the Regulation, namely CoronaVac COVID-19 Vaccine (Vero Cell), Inactivated ("CoronaVac") was received by the Secretary for Food and Health. The applicant provided further supplementary information, including Phase 3 clinical study data between 1 February 2021 and 15 February 2021 in accordance with the requirement specified under the "Guidance for Applications of Authorization of Vaccine under the Prevention and Control of disease (Use of Vaccines) Regulation (Cap. 599)". Details of the vaccine under application are summarized below:

Name of Vaccine:	CoronaVac COVID-19 Vaccine (Vero Cell), Inactivated 克爾來福新型冠狀病毒滅活疫苗(Vero 細胞)
Name and Address of Applicant:	Sinovac Biotech (Hong Kong) Limited Room 1906 19th Floor, Lucky Commercial Building, 103 Des Voeux Road West, Hong Kong
Name and Address of Manufacturer:	Sinovac Life Sciences Co., Ltd. No. 21, Tianfu Street, Daxing Biomedicine Industrial Base of Zhongguancun Science Park, Daxing District, Beijing, China
Composition:	Each vial contains 1 dose (0.5ml) of 600 SU of inactivated SARS-CoV-2 virus as antigen. The product is manufactured by inoculation of SARS-CoV-2 virus (CZ02 Strain) into African green Monkey Kidney Cell (Vero Cell), then the virus is incubated, harvested, inactivated, concentrated, purified and adsorbed by aluminum hydroxide. The vaccine is a milky-white suspension. Stratified precipitate may form which can be dispersed by shaking. The vaccine also contains the following excipients: Aluminum hydroxide (as adjuvant), disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride and water for injection. This product contains no preservatives.
Usage and Object of Vaccination:	The vaccine is indicated for active immunization against disease caused by SARS-CoV-2 virus. The target group for vaccination is susceptible people aged 18 and above. In Phase 3 clinical trial in Brazil, only 5.10% participants enrolled were 60 years and above, hence the efficacy evidence of people aged 60 and above is insufficient due to limited sample size. The subsequent clinical trials will be carried out for further evaluation of efficacy in this population. Data from conducted clinical trials showed that neutralizing antibodies would be induced after vaccination. When use CoronaVac among people aged 60 and above by relevant institutions, the

	health status and exposure risk of people aged 60 and above shall be considered.
Immunization Schedule and Dosage:	Two doses should be administered for primary immunization. The second dose is preferably given 28 days after the first dose. Each dose is 0.5ml. The vaccine should be administered by intramuscular injection in the deltoid region of the upper arm. Shake well before use. It has not been determined whether this product requires booster immunization.
Contraindication:	1. People with allergic history reaction to any component (active or inactive ingredients, or any material used in process) of the vaccine or similar vaccines; 2. Previous severe allergic reactions to the vaccine (e.g. acute anaphylaxis, angioedema, dyspnea, etc.); 3. People with severe neurological conditions (e.g. transverse myelitis, Guilllain-Barre syndrome, demyelinating diseases, etc.); 4. Patients with uncontrolled severe chronic diseases; 5. Pregnant and lactating women.
Precautions:	1. Due to the insufficient data of protection persistence, necessary protective measures should be taken in line with the COVID-19 pandemic. 2. Due to the insufficient data of efficacy in people aged 60 and above, when use CoronaVac among people aged 60 and above by relevant institutions, the health status and exposure risk of people aged 60 and above shall be considered. 3. This vaccine is strictly prohibited for intravenous injection. There is no safety and efficacy data of subcutaneous or intradermal injection. 4. Before use, check whether the packaging container, label, appearance and validity period meet the requirements or not. Do not use if there are cracks in the glass needle tube, spots, stains and scratches on the outer surface of the glass

	needle tube, label is not clear or more than the expiration date and abnormal appearance. 5. Avoid expose CoronaVac to the disinfectant during use. 6. This product should be stored at place out of reach of children. 7. Adequate treatment provisions, including epinephrine injection and emergency treatment, should be available for immediate use. Individuals should be observed for at least 30 minutes on site after vaccination. 8. Do not mix with other vaccines in the same syringe. 9. Do not freeze. It shall be administered immediately after open. 10. Patients with acute diseases, acute exacerbation of chronic diseases, severe chronic diseases, allergies and fever should be used with caution; if necessary, delay vaccination after doctor's evaluation. 11. Patients with diabetes and convulsions, epilepsy, encephalopathy or mental illness history or family history should be used with caution. 12. Patients with thrombocytopenia or hemorrhagic diseases, intramuscular injection of this product may cause bleeding, so it should be used with caution. 13. The safety and efficacy data of this product on people with impaired immune function (such as malignant tumor, nephrotic syndrome, AIDS patients) have not been obtained, and the vaccination of this product should be based on individual considerations. 14. The injection of human immunoglobulin should be given at least one month interval to avoid affecting the immune effect. 15. No clinical study has been carried out on the evaluation of immune response with other vaccines on the immunogenicity at the same time (before, after or at the same time). Professionals should be consulted when concomitant use.

	16. Do not use if there is any adverse reaction of nervous system after inoculation. 17. Like other vaccines, the protective effect may not reach 100% for all recipients.
Use in Special Population:	Women of childbearing age: the data collected of women with unexpected pregnancy after vaccination from clinical trials are very limited, which is not enough to decide the risk of adverse pregnancy outcomes after vaccination. Pregnant or lactating women: the clinical data of pregnant and lactating women are not available at present. People aged 60 and above: the immunogenicity and safety data from conducted clinical trials have been obtained, while the efficacy data from phase 3 clinical trial is insufficient.
Drug Interactions:	Concomitant use with other vaccines: no clinical study has been carried out on the evaluation of immune response with other vaccines on the immunogenicity at the same time (before, after or at the same time). Concomitant use with other drugs: immunosuppressive drugs, such as immunosuppressive drugs, chemotherapy drugs, antimetabolic drugs, alkylating agents, cytotoxic drugs, corticosteroid drugs, etc., may reduce the immune response to this product. Patients undergoing treatment: for patients undergoing treatment, please consult the professional doctors before use CoronaVac to avoid possible drug interactions.
Adverse Reactions:	Very common (>=10%), Common (1% ~ 10%, 1% was inclusive), Uncommon (0.1% ~ 1%, 0.1% was inclusive), Rare (0.01% ~ 0.1%, 0.01% was inclusive), Very rare (<0.01%): Adverse reactions at injection site: Very common: pain Common: swelling, pruritus, erythema, induration Uncommon: burn at injection site Systemic reactions:

	Very common: headache, fatigue Common: myalgia, nausea, diarrhea, arthralgia, cough, chills, pruritus, loss of appetite, rhinorrhea, sore throat, nasal congestion, abdominal pain Uncommon: vomit, hypersensitivity, abnormal skin and mucosa, fever, tremor, flushing, edema, dizziness, drowsiness Rare: muscle spasms, eyelid edema, nose bleed/epistaxis, abdominal distension, constipation, hyposmia, ocular congestion, hot flashes, hiccup, conjunctival congestion
Vaccine Platform and Mechanism of action:	Inactivated whole virion vaccine with aluminum hydroxide as the adjuvant.
Shelf Life and Special Precautions for Storage:	Store and transport between +2℃ and +8℃ and protect from light. Do not freeze. The shelf life of the vaccine is tentatively scheduled as 12 months.
Packaging Information:	40 vials per box

5. CoronaVac is currently approved by the following regulatory authorities:

- Indonesian National Agency for Drug and Food Control (NADFC, Badan Pengawas Obat dan Makanan Indonesia), Emergency Use Authorization granted on 11 January 2021;
- Turkish Medicines and Medical Devices Agency (TMMDA), Emergency Use Approval granted on 13 January 2021;
- Brazilian National Health Surveillance Agency (ANVISA), temporary authorization for emergency use granted on 17 January 2021; and
- The Institute of Public Health of Chile (ISP), emergency use authorization granted on 20 January 2021; and
- National Medical Products Administration (NMPA) of China, Conditional Authorization granted on 5 February 2021.

SAFETY, EFFICACY AND QUALITY OF CORONAVAC

6. The Advisory Panel conducted its meetings on 10 February 2021 and 16 February 2021 to review the safety, efficacy and quality of CoronaVac by taking into consideration of the submission from the applicant, published information, approval or authorization details and / or assessment results of overseas drug regulatory authorities, and post-marketing information. The Advisory Panel reviewed the following:

Vaccine Details

- CoronaVac is an inactivated vaccine to be administered intramuscularly as a course of 2 doses (each dose of 0.5ml contains 600SU inactivated SARS-CoV-2 virus as antigen) at an interval of 28 days for routine immunization. It is used for preventing COVID-19 caused by SARS-CoV-2 infection and suitable for people aged 18 years and over for immunization;

- the vaccine contains SARS-CoV-2 virus (CZ02 strain) inoculated into African green monkey kidney cell (Vero cell) which is inactivated and adsorbed by aluminum hydroxide. The vaccine is a milky-white suspension and contains the following excipients: aluminum hydroxide (as adjuvant), disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride and water for injection. The vaccine contains no preservatives;

Efficacy

- the two Phase 1/ 2 clinical studies conducted in Mainland China and the Phase 3 clinical study conducted in Brazil formed the basis for critical evaluation of efficacy of CoronaVac;

- two Phase 1/ 2 clinical studies were conducted in Mainland China to evaluate the safety and immunogenicity of CoronaVac in adults of 18 to 59 years of age (around 700 subjects) and 60 years of age or above (around 400 subjects) respectively and the results were published in the Lancet Infectious Diseases in November 2020 and February 2021 respectively as well;

- both Phase 1/ 2 clinical studies concluded a high seroconversion rate of neutralizing antibodies of CoronaVac when compared to those not vaccinated. The seroconversion rate of CoronaVac for either 0,14 days schedule and 0,28 days schedule in adults aged 18 to 59 years, and 0, 28 days schedule in adults of 60 years or above were demonstrated to be well above 90% after completion of the

two dose regimen, while the 0,28 days schedule demonstrated a relatively better immunogenicity profile;

- a Phase 3 placebo-controlled study was conducted in Brazil involving around 12 000 subjects who were healthcare professionals, with the data cut-off date of 16 December 2020 and demonstrating that CoronaVac was effective at preventing COVID-19 in adults of 18 years or above (including elderly subjects of 60 years or above) with a 0, 14 days vaccination schedule;

- the primary efficacy endpoint of vaccine efficacy against symptomatic COVID-19 cases was evaluated in nearly 10 000 healthcare professionals who worked in direct contact of people with possible or confirmed COVID-19 cases and had no history of possible or confirmed cases of COVID-19. The subjects had been followed up for at least two weeks after completion of two doses of vaccination at 0, 14 days interval. The vaccine efficacy was 50.65% (95% CI: 35.94 – 61.98), meaning a 50.65% reduction in the number of symptomatic COVID-19 cases in subjects who received the vaccine (85 cases out of 4 953 vaccinated subjects of 754.6 exposed person-year got symptomatic COVID-19) compared with subjects who received the placebo (168 cases out of 4 870 non-vaccinated subjects of 736.5 exposed person-year got symptomatic COVID-19). The data provided shown as meeting the minimum efficacy criteria for World Health Organization ("WHO") Emergency Use Listing ("EUL") assessment that the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%;

- the study also demonstrated a better vaccine efficacy in symptomatic COVID-19 cases of increasing severity. The vaccine efficacy for COVID-19 cases of WHO COVID-19 Clinical Progression Scale classification Score 3 (mild cases that need some type of assistance) or above was 83.7% (95% CI: 57.99, 93.67), Score 4 (moderate and severe cases) or above was 100.0% (95% CI: 56.37, 100), and severe cases was 100.0% (95% CI: 16.93, 100). For the vaccine efficacy against severe case, the lower bound of 95% CI did not meet the WHO criteria of >30% and probably due to low number of severe cases during the study;

- in a subgroup analysis conducted on different dosing intervals, the vaccine efficacy was 49.12% (95% CI: 33.01 – 61.36) for a dosing interval of below 21 days, and 62.32% (95% CI: 13.91, 83.51) for a dosing interval of equal to or more than 21 days. For the vaccine efficacy in dosing interval of 21 days or more, the

lower bound of 95% CI did not meet the WHO criteria of >30% and further study with large sample size would be necessary for confirmation. The results indeed indicated a better vaccine efficacy for a dosing interval of more than 21 days. The results supported the immunogenicity findings in the Phase 1/ 2 clinical studies and formed the basis of the Applicant's recommendation, in response to direct query by the Advisory Panel, of a dosing interval of 28 days in routine immunization, with which the Advisory Panel concurred based on the data available;

- in another subgroup analysis conducted in different age groups, the vaccine efficacy was 50.66% (95% CI: 35.75 – 62.11) in subjects of 18 to 59 years old, and 51.11% (95% CI: -166.93, 91.04) in subjects of 60 years old or above. The vaccine efficacy in elderly was not statistically significant due to limited number of elderly subjects (total 419 elderly subjects). While immunogenicity findings in elderly subjects in Phase 1/ 2 studies were positive, efficacy was demonstrated in elderly in Phase 3 study but the sample size was limited. The Advisory Panel recommended that the appropriateness of using CoronaVac in elderly of 60 years old or above should be advised by Joint Scientific Committee on Zoonotic and Emerging Diseases and Scientific Committee on Vaccine Preventable Diseases under the Centre for Health Protection;

- the neutralizing antibody geometric mean titre of the 600SU dose from the Phase 1 /2 trial in China, 28 days after all vaccination was 44.1 (95% CI: 37.2, 52.2) and the results suggesting the dosage of 600SU in this subsequent Phase 3 study as well as the current proposed dosage. The immunogenicity data of the Brazilian Phase 3 study was not available at the moment. The Advisory Panel advised to request the immunogenicity data for review when available;

- the Advisory Panel noted that Phase 3 studies were also conducted in Turkey and Indonesia. However, due to methodological and sample size issues, the Advisory Panel was unable to draw informative conclusions based on the data made available;

- there was data to demonstrate cross-neutralizing immunogenicity of CoronaVac on several SARS-CoV-2 virus strains found in the early stage of pandemic in China and including D614G mutant strains. There is currently no information regarding the immunogenicity against the new variant strains including the South African virus strain but was currently under investigation by Sinovac. The Advisory Panel advised to request Sinovac to provide the results for review, and the corresponding timeframe of results availability. In parallel, the Advisory

Panel also advised the Government should commission local immunogenicity studies against the prevailing strains and possible mutating strains;

- there was also preliminary information showing that the CoronaVac might induce mixed Th1 (initial) and Th2 (subsequent) type of cell-mediated immune response;

- there is currently no information regarding the effectiveness of the vaccine in certain populations, such as immunocompromised individuals, individuals previously infected with SARS-CoV-2 and pediatric population; and the effectiveness on protection against asymptomatic infection, viral transmission, mortality, or influenced by pandemic change or mutation of virus strains leading to antigenic change and vaccine resistance;

- the duration of protection is not known yet;

- as a condition of authorization as proposed in paragraph 8, the applicant is required to provide updated results from the planned, ongoing or future clinical studies, including but not limited to the Phase 3 studies in Brazil, Turkey and Indonesia, as well as cross-neutralizing immunogenicity study against different mutant strains of the virus, in order to address the unknown information and further substantiate the efficacy and safety of CoronaVac;

Safety

- the adverse reaction profile of CoronaVac as identified in clinical studies was summarized in the package insert and presented as follows. The very common (>1=10%) adverse reactions included injection site pain, headache, fatigue; common (1 to 10%) adverse reactions included injection site swelling, injection site pruritus, injection site erythema, injection site induration, myalgia, nausea, diarrhea, arthralgia, cough, chills, pruritus, loss of appetite, rhinorrhea, sore throat, nasal congestion, and abdominal pain; uncommon (0.1% to 1%) adverse reactions included burn at injection site, vomit, hypersensitivity, abnormal skin and mucosa, fever, tremor, flushing, edema, dizziness, drowsiness; rare (0.01% to 0.1%) adverse reactions included muscle spasms, eyelid edema, nasal congestion, abdominal distension, constipation, hyposmia, ocular congestion, hot flashes, hiccup, conjunctival congestion;

- overall, the reported adverse event profile from clinical studies was generally in line with other vaccines. The number of serious adverse events or death cases was limited and the majority of them were not considered related to the vaccine;

- the current available post-market adverse event data in China (as of 22 January 2021) demonstrated a low incidence of adverse events following immunization and generally aligned with the safety profile identified from clinical studies;

- regarding specific adverse events following immunization, the incidence rates of facial nerve palsy, Guillain Barre Syndrome (with data up to 2 February 2021) in vaccinated subjects were lower than the corresponding baseline incidence rate at the measuring time. Though there was no baseline incidence for generalized hypersensitivity, the incidence of hypersensitivity following immunization was about 6.2 per 100 000 that about one third of them have baseline history of allergic diseases. The Advisory Panel advised to request Sinovac to provide standardized and annualized event rates for ongoing assessment of the adverse events profile;

- by taking into consideration of the totality of scientific evidence and the above post-market safety information, the emerging safety profile was presently considered satisfactory. It was acknowledged that long term safety data, safety in certain populations (e.g. pregnancy, frail subjects, subjects with pre-existing autoimmune disease, etc.), interaction with other vaccines, and information of adverse reactions requiring longer follow up for detection was missing at this stage and ongoing assessment would be required. In this connection, the Advisory Panel noted that Risk Management Plan would be imposed for on-going monitoring of post-market safety information;

- taking reference to the considerations for evaluation of COVID-19 vaccines by the WHO, the available clinical safety and efficacy evidences relevant to CoronaVac were generally considered as satisfying the minimum clinical criteria for WHO Emergency Use Listing assessment;

Quality

- the manufacturer of the vaccine, Sinovac Life Sciences Co., Ltd. in China is demonstrated to comply with the Pharmaceutical Inspection Co-operation Scheme Good Manufacturing Practice standards or equivalent standards and the quality attributes of CoronaVac aligned with those approved and supplied in China and other countries;

- the applicant committed to continue the stability studies and submit the completed long-term stability data to support the shelf-life of the vaccine;

Risk Management Plan

- the applicant committed to implement a Hong Kong risk management plan ("RMP") as adopted from its global RMP that the current risk profile is summarized as follows:

    - Significant identified risks: None;
    - Significant potential risks: None;
    - Missing information: Use in people under 18 years old in China, other races and nationalities, people with immunodeficiency, pregnant and lactating women, elderly people with chronic diseases, patients with important organ damage; and study on combined vaccination with other vaccines;

- the Hong Kong RMP is considered sufficient in addressing the risks by conducting related pharmacovigilance measures. The applicant committed to submit the results of relevant post-authorization study as required by other drug regulatory authorities that aims to provide long term efficacy and safety data to address the unknown data gap. The applicant also committed to provide the periodic safety update report in order to review the post-market safety and to update the RMP when necessary;

- it is also noted that the Government will put in place a mechanism for monitoring any adverse events occurred to the recipients associated with the administration of the vaccines in Hong Kong;

- the applicant had provided a detailed package insert in Chinese (**Annex A**) and a bilingual brief edition package insert (**Annex B**) that summarized the indication, dosage, precautionary information, adverse events profile and storage condition of the vaccine. It will be made available for the healthcare professionals and members of the public. The Advisory Panel noted an English translated version of the detailed package insert will be available in due course.

ADVICE OF THE ADVISORY PANEL

7. After deliberation, the Advisory Panel considered that, based on the totality of scientific evidence on safety, efficacy and quality as available and the post-authorization measures to be taken, **the benefits of CoronaVac outweigh its risks for use** in Hong Kong

for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 18 years of age and older **during the current pandemic situation**.

CONDITIONS OF AUTHORIZATION

8. The Advisory Panel is of the view that for the purpose to ensure the benefits of CoronaVac continuously outweigh its risk, the applicant is recommended to comply with the following conditions if authorization is granted:

(a) the authorization applicant is required to report to the Department of Health ("DH") as soon as possible, and in any event no later than 72 hours after receipt of information, of any actions taken by overseas drug regulatory authorities on the authorized vaccine as a consequence of any safety concern of the authorized vaccine. Such overseas actions include but are not limited to the following actions arising from the safety concern of the authorized vaccine:

(i) recall, suspension or withdrawal of the authorized vaccine; or

(ii) addition or modification for safety reasons of a contraindication, warning or precaution statement in the product information;

(b) the authorization applicant is required to submit the final reports of all planned, on-going or future clinical studies of the authorized vaccine, which are part of its post-marketing commitments to overseas drug regulatory authorities of China or Brazil, to the DH for reassessment at the same time when the said reports are submitted to these overseas drug regulatory authorities. A summary of the conclusion of the clinical studies and the proposed follow-up actions have also to be provided. If there are any regulatory actions taken by these overseas drug regulatory authorities in view of the results of the clinical studies of the authorized vaccine, the authorization applicant is required to inform the DH of the actions as soon as possible, and in any event no later than 72 hours after the actions have been taken;

(c) the authorization applicant is required to submit periodic safety update reports, summary safety report, or their equivalents, of the authorized vaccine to the DH every six months or at an interval as may be notified by the Secretary for Food and Health;

(d) the authorization applicant is required to report all serious or unexpected adverse events following immunization of the authorized vaccine occurring in Hong Kong to the DH in accordance with available guidance for COVID-19 vaccines;

(e) the authorization applicant is required to implement the Risk Management Plan ("RMP") for the authorized vaccine in Hong Kong as it has proposed. The authorization applicant is also required to update the local RMP in accordance with its global RMP when it is modified and implement accordingly;

(f) the authorization applicant is required to report to the DH any significant changes or any conditions relating to the manufacturer or to the manufacture of the vaccine which may affect the quality, safety or efficacy of the authorized vaccine without undue delay;

(g) upon commencement of recall of the authorized vaccine, the authorization applicant is required to report the recall and submit pertinent product information relating to that recall to the DH and to comply with available guidance for pharmaceutical products, including the current Pharmaceutical Products Recall Guidelines issued by the Drug Office of the DH;

(h) the authorization applicant is required to document any defect impacting the quality of the authorized vaccine released for sale or distribution;

(i) the authorization applicant is required to submit further quality data and to the DH at the same time when the said quality data or relevant quality documents reports are submitted to China or Brazil drug regulatory authorities as part of its post-authorization commitments, and to update the relevant quality documents of the authorized vaccine, if applicable, in order to continue to assure the quality of the authorized vaccine;

(j) the authorization applicant must provide the certificate of analysis issued by the manufacturer for each batch of the vaccine supplied to Hong Kong;

(k) the authorization applicant should provide a lot release certificate issued by national regulatory authority ("NRA") or batch release certificate issued by accredited laboratory authorized by NRA or certificate of

analysis issued by an independent accredited laboratory for the batch of the vaccine supplied to Hong Kong as directed by the DH; and

(l) the authorization applicant is required to submit relevant information and justifications / supporting evidence to the DH for any changes related to the authorized vaccine, including but not limited to the content of package insert, label, or any quality attributes. The changes should only be implemented after endorsement by the Secretary for Food and Health is obtained.

Advisory Panel on COVID-19 Vaccines
17 February 2021

References:

1. Yanjun Zhang, Gang Zeng, Hongxing Pan, et. al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in health adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infectious Disease, November 2020.

2. Zhiwei Wu, Yaling Hu, Miao Xu, et. al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 60 years and older: a randomised, double blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infectious Disease, February 2021.

3. World Health Organization. Considerations for evaluation of COVID 19 vaccines. Points to consider for manufacturers of COVID 19 vaccines. Version 25 November 2020.

核准日期：

修改日期：

新型冠状病毒灭活疫苗（Vero 细胞）说明书

本品为附条件批准上市，请仔细阅读说明书并在医师指导下使用

【药品名称】

通用名称：新型冠状病毒灭活疫苗（Vero 细胞）

商品名称：克尔来福（CoronaVac）

英文名称：COVID-19 Vaccine（Vero Cell），Inactivated

汉语拼音：Xinxing Guanzhuang Bingdu Miehuoyimiao (Vero Xibao)

【成分】

本品系用新型冠状病毒（CZ02 株）接种非洲绿猴肾细胞（简称 Vero 细胞），经培养、收获病毒液、灭活病毒、浓缩、纯化和氢氧化铝吸附制成。本品不含防腐剂。

主要成分：灭活的新型冠状病毒（CZ02 株）。

佐剂：氢氧化铝佐剂。

辅料：磷酸氢二钠十二水合物、磷酸二氢钠一水合物、氯化钠。

【性状】

为乳白色混悬液体，可因沉淀而分层，易摇散。

【接种对象】

本品适用于 18 岁及以上人群的预防接种。

本品境外III期临床试验中 60 岁及以上人群所占比例较低（5.10%），60 岁及以上人群保护效力证据尚不充分。后续临床试验将继续开展 60 岁及以上人群保护效力研究，进一步获取该人群保护效力证据。已有的临床试验数据显示，60 岁及以上人群接种本品后产生一定程度的中和抗体。疾病预防控制相关机构接种使用时，需结合 60 岁及以上人群健康状态和暴露风险，评估接种本品的必要性。

【作用与用途】

本品适用于预防新型冠状病毒（SARS-CoV-2）感染所致的疾病（COVID-19）。

本品为基于境外III期临床保护效力试验两个月的结果获得附条件批准上市，暂未获得最终分析数据，有效性和安全性结果尚待进一步最终确证。

【规格】

0.5 ml/支（瓶），每 1 次人用剂量为 0.5ml，含灭活新型冠状病毒抗原 600SU。

【免疫程序和剂量】

本品基础免疫为 2 剂次，间隔 28 天；每一次人用剂量为 0.5ml。

推荐的接种途径为肌肉注射，最佳部位为上臂三角肌，注射前须摇匀。

尚未确定本品是否需要进行加强免疫。

【不良反应】

在境内外开展的 4 项临床试验中评价了本品的安全性，分别为在境内 18~59 岁和 60 岁及以上人群中开展的随机、双盲、安慰剂对照的 I/II期临床试验；在巴西 18 岁及以上医务人员中开展的随机、双盲、安慰剂对照的III期临床保护效力试验，以及在境内开展的不同生产规模和不同人群的IIIb 期临床桥接试验。每剂次接种后 0~7 天进行系统性安全性随访观察，8-14/28 天采取受试者主动报告与研究者定期随访的方式收集不良事件，同时关注全程接种后 12 个月内发生的严重不良事件。

1.本品临床试验不良反应发生情况总述

本品在境内外的系列临床试验共入组 14,572 名 18 岁及以上受试者，其中

7,658 名受试者至少接种 1 剂本品。所有受试者均已完成全程免疫后至少 28 天的随访，长期安全性访视尚在进行中。

按国际医学科学组织委员会（CIOMS）推荐不良反应的发生率分类：十分常见（≥10%），常见（1%～10%，含 1%），偶见（0.1%～1%，含 0.1%），罕见（0.01%～0.1%，含 0.01%），十分罕见（＜0.01%）。按照 CIOMS 标准，汇总本品所有不良反应，进行如下描述：

（1）接种部位不良反应

十分常见：疼痛

常见：肿胀、瘙痒、红斑、硬结

偶见：接种部位发热

（2）全身不良反应

十分常见：头痛、疲乏

常见：肌痛、恶心、腹泻、关节痛、咳嗽、寒战、瘙痒、食欲减退、流涕、咽痛、鼻充血、腹痛

偶见：呕吐、超敏反应、皮肤粘膜异常、发热、震颤、潮红、水肿、头晕、嗜睡

罕见：肌痉挛、眼睑水肿、鼻衄、腹胀、便秘、嗅觉减退、眼充血、潮热、呃逆、结膜充血

（3）不良反应严重程度

本品系列临床试验中观察到的不良反应严重程度以 1 级（轻度）为主，3 级及以上不良反应的发生率为 1.31%。

3 级及以上不良反应为接种部位疼痛、咳嗽、发热、头痛、咽痛、腹痛、头晕、嗜睡。

（4）严重不良事件（SAE）

截至 2021 年 2 月 3 日，尚未发现经研究者判断与接种本品有关的严重不良

事件。

2.本品境内外临床试验不良反应发生情况

（1）境内临床试验

境内 I/II期以及IIIb 期桥接临床试验共入组 18 岁及以上受试者 2203 名，1452 名受试者至少接种 1 剂本品（I/II期临床试验中剂量），其中 18~59 岁 1067 人（73.48%）；60 岁及以上 385 人（26.52%）。所有受试者均已完成全程免疫后至少 28 天的随访，长期安全性随访尚在进行中。

本品全程接种后 28 天内不良反应以征集性反应为主；成人非征集性不良反应发生率为 1.50%，老年人非征集性不良反应发生率为 1.30%。18~59 岁人群中 2 名受试者接种本品后发生了 3 级不良反应，3 级不良反应发生率为 0.14%，症状分别为发热和头痛。

I/II期临床试验及IIIb 期桥接临床试验研究人群安全性数据详见表 1。

表 1 境内 I/II期以及桥接临床试验不良反应发生情况 n（%）

年龄分组	**18~59 岁**				**≥60 岁**		
免疫程序	**0,14 天**		**0,28 天**		**0,14 天**	**0,28 天**	
试验分组	**本品 (N=923) n(%)**	**安慰剂 (N=84) n(%)**	**本品 (N=144) n(%)**	**安慰剂 (N=83) n(%)**	**本品 (N=260) n(%)**	**本品 (N=125) n(%)**	**安慰剂 (N=73) n(%)**
总体不良反应	**159(17.23)**	**15(17.86)**	**26(18.06)**	**14(16.87)**	**15(5.77)**	**25(20.00)**	**15(20.55)**
征集性不良反应	**152(16.47)**	**15(17.86)**	**26(18.06)**	**13(15.66)**	**13(5.00)**	**24(19.20)**	**12(16.44)**
全身不良反应	93(10.08)	10(11.90)	16(11.11)	7(8.43)	8(3.08)	12(9.60)	9(12.33)
乏力	25(2.71)	7(8.33)	10(6.94)	2(2.41)	2(0.77)	4(3.20)	1(1.37)
发热	28(3.03)	1(1.19)	4(2.78)	2(2.41)	3(1.15)	4(3.20)	1(1.37)
肌肉痛	14(1.52)	1(1.19)	2(1.39)	3(3.61)	0(0.00)	2(1.60)	2(2.74)
腹泻	19(2.06)	1(1.19)	2(1.39)	1(1.20)	4(1.54)	1(0.80)	1(1.37)
头痛	13(1.41)	1(1.19)	3(2.08)	0(0.00)	1(0.38)	0(0.00)	0(0.00)
咳嗽	11(1.19)	0(0.00)	3(2.08)	0(0.00)	1(0.38)	1(0.80)	1(1.37)

年龄分组	18~59 岁				≥60 岁		
免疫程序	0,14 天		0,28 天		0,14 天	0,28 天	
试验分组	本品 (N=923) n(%)	安慰剂 (N=84) n(%)	本品 (N=144) n(%)	安慰剂 (N=83) n(%)	本品 (N=260) n(%)	本品 (N=125) n(%)	安慰剂 (N=73) n(%)
恶心	7(0.76)	0(0.00)	2(1.39)	0(0.00)	0(0.00)	1(0.80)	3(4.11)
皮肤粘膜异常	4(0.43)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
厌食	2(0.22)	0(0.00)	0(0.00)	0(0.00)	2(0.77)	1(0.80)	0(0.00)
呕吐	2(0.22)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
急性过敏反应	0(0.00)	0(0.00)	1(0.69)	0(0.00)	0(0.00)	1(0.80)	0(0.00)
局部不良反应	**77(8.34)**	**7(8.33)**	**15(10.42)**	**9(10.84)**	**7(2.69)**	**15(12.00)**	**3(4.11)**
疼痛	71(7.69)	7(8.33)	15(10.42)	9(10.84)	6(2.31)	15(12.00)	3(4.11)
瘙痒	6(0.65)	0(0.00)	0(0.00)	0(0.00)	1(0.38)	0(0.00)	0(0.00)
肿胀	6(0.65)	0(0.00)	0(0.00)	1(1.20)	0(0.00)	1(0.80)	0(0.00)
红晕	2(0.22)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(1.37)
硬结	1(0.11)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
非征集性不良反应	16(1.73)	0(0.00)	0(0.00)	2(2.41)	2(0.77)	3(2.40)	5(6.85)

（2）境外临床试验

境外III期临床试验共入组 18 岁及以上受试者 12,396 名，6202 名受试者接种至少 1 剂本品，其中，60 岁及以上 316 人（5.10%）。所有受试者均已完成全程免疫后至少 28 天的随访，长期安全性随访尚在进行中。

III期临床试验 18 岁以上人群接种本品的征集性不良反应发生情况详见表 2。本品非征集性不良反应发生率分别为 36.83%，症状主要为流涕（7.01%）、咽痛（6.93%）、鼻充血（2.74% ）、腹痛（1.34%）、头晕（0.66%）。

本品所有不良反应严重程度均以 1 级和 2 级为主，严重程度为 3 级的不良反应发生率为 1.58%。非征集性不良反应中较征集性新增严重程度为 3 级的症状包括：咽痛（0.03%）、腹痛（0.03%）、头晕（0.02%）、嗜睡（0.02%）。

表 2 巴西III期临床试验征集性不良反应发生情况 n（%）

不良反应名称	本品(N=6202) n(%)	安慰剂 (N=6194) n(%)
征集性不良反应	4536(73.14)	3714(59.96)
3 级	66(1.06)	69(1.11)
局部不良反应	3815(61.51)	2143(34.6)
3 级	4(0.06)	1(0.02)
疼痛	3742(60.34)	2014(32.52)
3 级	4(0.06)	1(0.02)
肿胀	359(5.79)	130(2.1)
3 级	0(0.00)	0(0.00)
瘙痒	263(4.24)	181(2.92)
3 级	0(0.00)	0(0.00)
红斑	241(3.89)	89(1.44)
3 级	0(0.00)	0(0.00)
硬结	235(3.79)	67(1.08)
3 级	0(0.00)	0(0.00)
全身不良反应	2999(48.36)	2947(47.58)
3 级	64(1.03)	69(1.11)
头痛	2128(34.31)	2157(34.82)
3 级	34(0.55)	46(0.74)
疲乏	989(15.95)	922(14.89)
3 级	12(0.19)	13(0.21)
肌痛	727(11.72)	648(10.46)
3 级	5(0.08)	10(0.16)
恶心	490(7.9)	522(8.43)
3 级	6(0.10)	6(0.10)
腹泻	492(7.93)	501(8.09)

3 级	8(0.13)	7(0.11)
关节痛	353(5.69)	321(5.18)
3 级	8(0.13)	3(0.05)
咳嗽	343(5.53)	322(5.2)
3 级	0(0.00)	0(0.00)
寒战	309(4.98)	313(5.05)
3 级	1(0.02)	1(0.02)
瘙痒	263(4.24)	225(3.63)
3 级	1(0.02)	0(0.00)
食欲减退	217(3.5)	243(3.92)
3 级	0(0.00)	0(0.00)
呕吐	61(0.98)	61(0.98)
3 级	3(0.05)	3(0.05)
超敏反应	58(0.94)	58(0.94)
3 级	2(0.03)	2(0.03)
皮肤粘膜异常	49(0.79)	42(0.68)
3 级	1(0.02)	0(0.00)
发热	9(0.15)	4(0.06)
3 级	0(0.00)	0(0.00)

【禁忌】

1. 对本品中的活性成分、任何一种非活性成分、生产工艺中使用的物质过敏者，或以前接种本品或同类疫苗时出现过敏者。

2. 既往发生过疫苗严重过敏反应者（如急性过敏反应、血管神经性水肿、呼吸困难等）。

3. 患有严重神经系统疾病者（如横贯性脊髓炎、格林巴利综合症、脱髓鞘疾病等）。

4. 未控制的严重慢性病患者。

5. 妊娠期及哺乳期妇女。

【注意事项】

1. 目前暂未获得本品的保护持久性数据，接种后仍需根据疫情防控需要采取必要的防护措施。

2. 目前本品对 60 岁及以上人群的保护效力数据有限，疾病预防控制相关机构接种使用时，需结合该人群健康状态和暴露风险，评估接种本品的必要性。

3. 本品严禁血管内注射。尚无本品采用皮下或皮内注射的安全性和有效性数据。

4. 使用前应检查包装容器、标签、外观、有效期是否符合要求，如玻璃针管有裂纹，玻璃针管外表面有斑点、污点、擦痕，标签不清或超过有效期时限及外观异常等均不得使用。

5. 开启疫苗瓶和注射时，切勿使消毒剂接触疫苗。

6. 本品须置于儿童不可触及处。

7. 接种现场应备有肾上腺素等药物和设备，以备发生严重急性过敏反应时急救用。在接种本品后应在现场观察至少 30 分钟。

8. 本品不能与其他疫苗在同一注射器内混合。

9. 本品严禁冻结。开启后应立即使用。

10. 患急性疾病、慢性疾病的急性发作期、严重慢性疾病、过敏体质和发热者需慎用；必要时经医生评估后延迟接种。

11. 糖尿病患者及有惊厥、癫痫、脑病或精神疾病史或家族史者需慎用。

12. 患有血小板减少症或者出血性疾病者，肌肉注射本品可能会引起出血，需慎用。

13. 尚未获得本品对免疫功能受损者（例如恶性肿瘤、肾病综合征、艾滋病患者）的安全性和有效性数据，此类人群接种本品应基于个体化考虑。

14. 注射人免疫球蛋白者应至少间隔 1 个月以上接种本品，以免影响免疫效果。

15. 尚未进行同期（先、后或同时）接种其它疫苗对本品免疫原性影响的临床研究，同期接种其它疫苗时应咨询专业医师。

16. 接种本品后出现任何神经系统不良反应者，禁止再次使用。

17. 与其它疫苗一样，无法确保本品对所有接种者均产生保护作用。

【特殊人群用药】

1.育龄期妇女：在临床试验中接种本品后意外妊娠的妇女中收集到的数据非常有限，尚不足以判断接种本品后可能导致发生不良妊娠结局的风险。

2.妊娠期或哺乳期女性：目前尚未获得孕妇及哺乳期妇女使用本品的临床试验数据。

3. 60 岁及以上人群：目前已在境内临床试验中获得该人群接种本品的免疫原性与安全性数据，境外III期临床试验中获得保护效力证据尚不充分。

【药物相互作用】

1.与其他疫苗同时接种：本品尚未进行同期（先、后或同时）接种其他疫苗对本品免疫原性影响的临床研究。

2. 与其它药物伴随使用：具有免疫抑制作用的药物，如免疫抑制剂、化疗药物、抗代谢药物、烷化剂、细胞毒素类药物、皮质类固醇类药物等，可能会降低机体对本品的免疫应答。

3.正在接受治疗的患者：对于正在使用药物的人群，为避免可能的药物间相互作用，接种本品前建议咨询专业医师。

【临床试验】

1.保护效力试验结果

本品关键性III期临床试验采用多中心、随机、双盲、安慰剂平行对照的设计，分别在巴西 18 岁及以上医务人员和土耳其 18~59 岁健康人群中开展，用于评估

本品在高危人群（接诊 COVID-19 患者的医务人员）和普通人群中的保护效力。主要研究假设为：在上述人群中按照 0,14 天程序接种 2 剂本品 14 天后，相较于安慰剂组的保护效力（VE）95%置信区间下限大于 30%。巴西疫苗保护效力的主要分析方法基于人年发病率计算保护率，土耳其疫苗保护效力则基于发病率计算保护率。所有有效终点病例均经过终点判定委员会确认。

（1）巴西III期临床试验

巴西 III 期临床试验目标人群为接诊 COVID-19 患者的医务人员，试验共入组 12,396 名受试者，获得 253 例监测期有效病例。按照 0,14 天程序接种 2 剂本品 14 天后预防由新型冠状病毒所致疾病（COVID-19）的保护效力：对住院、重症及死亡新冠病例的保护效力为 100.00%（95%CI：56.37-100.00），对有明显症状且需要就医的新冠病例保护效力为 83.70%（95%CI：57.99-93.67），对包括轻微症状不需就医的所有新冠病例保护效力为 50.65%（95%CI：35.66-62.15）。接种本品受试者平均随访时间为 70.3±25.6 天，随访中位时间为 73.0 天。

表 3. 巴西III期临床试验 2 剂免疫 14 天后对 COVID-19 的保护效果（PPS）

分组	本品（N=4953）			安慰剂（N=4870）			VE (%) (95%CI)
	发病人数	暴露人年数	人年发病率(%)	发病人数	暴露人年数	人年发病率(%)	
新冠病例	85	754.6	11.03	168	736.5	22.34	50.65 (35.66, 62.15)
WHO3 级及以上*	5	755.6	0.66	30	737.9	4.07	83.70 (57.99, 93.67)
WHO4 级及以上#	0	755.6	0.00	10	738.2	1.35	100.00 (56.37, 100.00)

*WHO-3 级及以上：需要就医的新冠病例；

WHO-4 级及以上：需要住院治疗、重症及死亡病例，其中重症病例 5 例，死亡病例 1 例。

VE：保护效力

（2）土耳其III期临床试验

土耳其 III 期临床试验目标人群为处于高风险的医护人员（K-1）和处于正常风险的一般人群（K-2），截至 2020 年 12 月 23 日，共完成 K-1 队列受试者入组 918 例，K-2 队列入组受试者 6453 例，总计 7371 例；其中 1322 例受试者完成两剂接种并进入第二剂接种后 14 天观测期。基于 29 例病例的分析结果显示，按照

0,14 天程序接种 2 剂本品 14 天后预防 COVID-19 的保护效力为 91.25%（95%CI：71.25- 97.34），结果详见表 4。

表 4. 土耳其III期临床试验 2 剂免疫 14 天后对 COVID-19 的保护效果

试验分组指标	本品（N=752）		安慰剂（N=570）		VE (%) (95%CI
	发病人数	发病率（%）	发病人数	发病率（%）	
COVID-19	3	0.40	26	4.56	91.25 (71.25- 97.34)

2.免疫原性

本品免疫原性终点包括血清中和抗体阳转率和几何平均滴度（GMT）。阳转定义为免疫前中和抗体滴度<1:8 者，免疫后中和抗体滴度≥1:8；或免疫前中和抗体滴度≥1:8 者，免疫后中和抗体滴度达 4 倍及以上增长。中和抗体测定采用细胞培养微量中和试验（细胞病变抑制法）确定。

表 5. 18 岁及以上人群不同免疫程序中和抗体阳转率和 GMT（95%CI）（PPS）

研究人群	试验分期（免疫程序）	指标	2 剂免后 14 天	2 剂免后 28 天
18~59 岁成人	II期（0,14 天）	N	118	118
		阳性人数(阳转率%)	109(92.37)(86.01,96.45)	111 (94.07)(88.16, 97.58)
		GMT	27.6(22.7,33.5)	23.8(20.5, 27.7)
	II期（0,28 天）	N	-	117
		阳性人数(阳转率%)	-	114(97.44)(92.69,99.47)
		GMT	-	44.1(37.2,52.2)
60 岁及以上老年人	II期（0,28 天）	N	-	98
		阳性人数(阳转率%)	-	96 (97.96)(92.82, 99.75)
		GMT	-	42.2(35.2, 50.6)

3.交叉中和

基于 80 名 26~45 岁受试者按照 0,14 天程序免疫前后的血清，对境内外流行的 12 种新冠病毒株（CZ02、WZL、WGF、ZJY、SSH、JWL、ZYF、HAC、HJL、ZXZ、QHF 和 NOOR）进行血清交叉中和检测。采用细胞培养微量中和试验（细胞病变法）进行血清中和抗体检测。结果显示，本品免疫后诱导机体产生的抗体具有交叉中和不同新冠病毒株（含 D614G 突变株）的能力，阳转率在 80.00%~100.00%之间，GMT 在 15.4-46.7 之间。

【贮藏】

于 2～8℃避光保存和运输。

【有效期】

暂定 12 个月。

【包装】

本品为预充式注射器或西林瓶包装，1 支（瓶）/盒。

【执行标准】

YBS00152021

【批准文号】

【药品上市许可持有人】

名称：北京科兴中维生物技术有限公司

注册地址：北京市大兴区中关村科技园大兴生物医药产业基地天富街 21 号 1 号楼

【生产企业】

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Annex B

核准日期:

修改日期:

新型冠状病毒灭活疫苗（Vero 细胞）说明书（简要版）

本品为附条件批准上市，请仔细阅读说明书并在医师指导下使用

【药品名称】

通用名称：新型冠状病毒灭活疫苗（Vero细胞）

商品名称：克尔来福（CoronaVac）

英文名称：COVID-19 Vaccine (Vero Cell), Inactivated

汉语拼音： Xinxing Guanzhuang Bingdu Miehuoyimiao (Vero Xibao)

【成分】

主要成分：灭活的新型冠状病毒（CZ02 株）。

佐剂：氢氧化铝佐剂。

辅料：磷酸氢二钠十二水合物、磷酸二氢钠一水合物、氯化钠。

【性状】

为乳白色混悬液体，可因沉淀而分层，易摇散。

【接种对象】

本品适用于 18 岁及以上人群的预防接种。

本品境外 III 期临床试验中 60 岁及以上人群所占比例较低（5.10%），60 岁及以上人群保护效力证据尚不充分。后续临床试验将继续开展 60 岁及以上人群保 护效力研究，进一步获取该人群保护效力证据。已有的临床试验数据显示，60 岁及以上人群接种本品后产生一定程度的中和抗体。疾病预防控制相关机构接种使用时，需结合 60 岁及以上人群健康状态和暴露风险，评估接种本品的必要性。

【作用与用途】

本品适用于预防新型冠状病毒（SARS-CoV-2）感染所致的疾病（COVID-19）。本品为基于境外 III 期临床保护效力试验两个月的结果获得附条件批准上市，暂未获得最终分析数据，有效性和安全性结果尚待进一步最终确证。

【规格】

0.5 ml/支（瓶），每 1 次人用剂量为 0.5mL 含灭活新型冠状病毒抗原 600SU。

【免疫程序和剂量】

本品基础免疫为 2 剂次，间隔 28 天；每一次人用剂量为 0.5ml。

推荐的接种途径为肌肉注射，最佳部位为上臂三角肌，注射前须摇匀。

尚未确定本品是否需要进行加强免疫。

【不良反应】

在境内外开展的 4 项临床试验中评价了本品的安全性，分别为在境内 18-59 岁和 60 岁及以上人群中开展的随机、双盲、安慰剂对照的 I/II 期临床试验；在巴西 18 岁及以上医务人员中开展的随机、双盲、安慰剂对照的 III 期临床保护效力试验，以及在境内开展的不同生产规模和不同人群的 IIIb 期临床桥接试验。每 剂次接种后 0~7 天进行系统性安全性随访观察，8-14/28 天采取受试者主动报告与研究者定期随访的方式收集不良事件，同时关注全程接种后 12 个月内发生的严重不良事件。

本品临床试验不良反应发生情况总述

本品在境内外的系列临床试验共入组 14,572 名 18 岁及以上受试者，其中 7,658 名受试者至少接种 1 剂本品。所有受试者均已完成全程免疫后至少 28 天的随访，长期安全性访视尚在进行中。

按国际医学科学组织委员会（CIOMS）推荐不良反应的发生率分类：十分常见（≥10%），常见（1%～10%，含 1%），偶见（0.1%～1%，含 0.1%），罕见（0.01%～0.1%，含 0.01%），十分罕见（＜0.01%）。按照 CIOMS 标准，汇总本品所有不良反应，进行如下描述：

1. 接种部位不良反应

十分常见：疼痛

常见：肿胀、瘙痒、红斑、硬结

偶见：接种部位发热

2. 全身不良反应

十分常见：头痛、疲乏

常见：肌痛、恶心、腹泻、关节痛、咳嗽、寒战、瘙痒、食欲减退、流涕、 咽痛、鼻充血、腹痛

偶见：呕吐、超敏反应、皮肤粘膜异常、发热、震颤、潮红、水肿、头晕、 嗜睡

罕见：肌痉挛、眼睑水肿、鼻衄、腹胀、便秘、嗅觉减退、眼充血、潮热、呃逆、结膜充血

3. 不良反应严重程度

本品系列临床试验中观察到的不良反应严重程度以 1 级（轻度）为主，3 级及以上不良反应的发生率为 1.31%。

3 级及以上不良反应为接种部位疼痛、咳嗽、发热、头痛、咽痛、腹痛、头晕、嗜睡。

4. 严重不良事件（SAE）

截至 2021 年 2 月 3 日，尚未发现经研究者判断与接种本品有关的严重不良事件。

各项临床试验不良反应发生情况详见本品完整版说明书。

【禁忌】

1. 对本品中的活性成分、任何一种非活性成分、生产工艺中使用的物质过敏者，或以前接种本品或同类疫苗时出现过敏者。

2. 既往发生过疫苗严重过敏反应者（如急性过敏反应、血管神经性水肿、呼吸困难等）。

3. 患有严重神经系统疾病者（如横贯性脊髓炎、格林巴利综合症、脱髓鞘疾病等）。

4. 未控制的严重慢性病患者。

5. 妊娠期及哺乳期妇女。

【注意事项】

1. 目前暂未获得本品的保护持久性数据，接种后仍需根据疫情防控需要采取必要的防护措施。

2. 目前本品对 60 岁及以上人群的保护效力数据有限，疾病预防控制相关机构接种使用时，需结合该人群健康状态和暴露风险，评估接种本品的必要性。

3. 本品严禁血管内注射。尚无本品采用皮下或皮内注射的安全性和有效性数据。

4. 使用前应检查包装容器、标签、外观、有效期是否符合要求，如玻璃针管有裂纹，玻璃针管外表面有斑点、污点、擦痕，标签不清或超过有效期时限及 外观异常等均不得使用。

5. 开启疫苗瓶和注射时，切勿使消毒剂接触疫苗。

6. 本品须置于儿童不可触及处。

7. 接种现场应备有肾上腺素等药物和设备，以备发生严重急性过敏反应时急救用。在接种本品后应在现场观察至少 30 分钟。

8. 本品不能与其他疫苗在同一注射器内混合。

9. 本品严禁冻结。开启后应立即使用。

10. 患急性疾病、慢性疾病的急性发作期、严重慢性疾病、过敏体质和发热者需慎用；必要时经医生评估后延迟接种。

11. 糖尿病患者及有惊厥、癫痫、脑病或精神疾病史或家族史者需慎用。

12. 患有血小板减少症或者出血性疾病者，肌肉注射本品可能会引起出血，需慎用。

13. 尚未获得本品对免疫功能受损者（例如恶性肿瘤、肾病综合征、艾滋病患者）的安全性和有效性数据，此类人群接种本品应基于个体化考虑。

14. 注射人免疫球蛋白者应至少间隔 1 个月以上接种本品，以免影响免疫效果。

15. 尚未进行同期（先、后或同时）接种其它疫苗对本品免疫原性影响的临床研究，同期接种其它疫苗时应咨询专业医师。

16. 接种本品后出现任何神经系统不良反应者，禁止再次使用。

17. 与其它疫苗一样，无法确保本品对所有接种者均产生保护作用。

【特殊人群用药】

1. 育龄期妇女：在临床试验中接种本品后意外妊娠的妇女中收集到的数据非常有限，尚不足以判断接种本品后可能导致发生不良妊娠结局的风险。

2. 妊娠期或哺乳期女性：目前尚未获得孕妇及哺乳期妇女使用本品的临床试验数据。

3. 60 岁及以上人群：目前已在境内临床试验中获得该人群接种本品的免疫原性与安全性数据，境外 III 期临床试验中获得保护效力证据尚不充分。

【药物相互作用】

1. 与其他疫苗同时接种：本品尚未进行同期（先、后或同时）接种其他疫苗对本品免疫原性影响的临床研究。

2. 与其它药物伴随使用：具有免疫抑制作用的药物，如免疫抑制剂、化疗药物、抗代谢药物、烷化剂、细胞毒素类药物、皮质类固醇类药物等，可能会降低机体对本品的免疫应答。

3. 正在接受治疗的患者：对于正在使用药物的人群，为避免可能的药物间相互作用，接种本品前建议咨询专业医师。

【贮藏】

于 2～8℃避光保存和运输。

【有效期】

暂定 12 个月。

【包装】

本品为预充式注射器或西林瓶包装，1 支（瓶）/盒。

【执行标准】

YBS00152021

【批准文号】

【药品上市许可持有人】

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Annex B

Approved Date:

Revised Date:

COVID-19 Vaccine (Vero Cell), Inactivated (Brief Edition)

This is the Conditional Marketing Authorization, please refer to the instruction and use under the doctor guidance.

【NAME OF THE MEDICAL PRODUCT】

Generic Name: COVID-19 Vaccine (Vero Cell), Inactivated

Trade Name: CoronaVac

English Name: COVID-19 Vaccine (Vero Cell), Inactivated

Chinese Phonetic Alphabet: Xinxing Guanzhuang Bingdu Miehuoyimiao (Vero Xibao)

【COMPOSITION】

Active ingredient: Inactivated SARS-CoV-2 Virus (CZ02 strain)

Adjuvant: Aluminum hydroxide

Excipients: disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride.

【DESCRIPTION】

CoronaVac is a milky-white suspension. Stratified precipitate may form which can be dispersed by shaking.

【TARGET GROUPS FOR VACCINATION】

Susceptible people aged 18 and above.

In Brazil phase III clinical trial, only 5.10% participants enrolled was 60 years and above, hence, the efficacy evidence of people aged 60 and above is insufficient. The subsequent clinical trials will be

carried out for further evaluation of efficacy in this population. Data from conducted clinical trials showed that neutralizing antibodies would be induced after vaccination. When use CoronaVac among people aged 60 and above by relevant institutions, the health status and exposure risk of people aged 60 and above shall be considered.

【THERAPEUTIC INDICATION】

CoronaVac is indicated for active immunization against diseases caused by SARS-CoV-2 virus.

Based on the efficacy results for two months from overseas phase III clinical trial, a conditional marketing authorization (CMA) for CoronaVac has been issued. The final efficacy data are not yet available; hence, the efficacy and safety results need to be further confirmed.

【PRESENTATION】

Each vial (syringe) contains 0.5 mL. Single dose of 0.5 mL contains 600SU of inactivated SARS-CoV-2 virus as antigen.

【ADMINISTRATION AND SCHEDULE】

Two doses should be administered for primary immunization. The second dose is preferably given 28 days after the first dose. 0.5 mL per dose.

CoronaVac should be administered by intramuscular injection in the deltoid region of the upper arm. Shake well before use.

It has not been determined whether this product requires booster immunization.

【ADVERSE REACTIONS】

The safety of CoronaVac was evaluated in 4 clinical trials conducted domestic and overseas, including randomized, double-blind, placebo-controlled phase I/II clinical trials in people aged 18-59 years and in elderly aged 60 years and above, a phase III clinical efficacy trial in Brazilian health professionals aged 18 years and above, and a phase IIIb bridging trial in different production scales and different populations. Systematic safety observation was carried out within 7 days after each vaccination, and

adverse events were collected by voluntary report of subjects and regular follow-up of investigators on 8-14/28 days, long-term of serious adverse events within 12 months after the full vaccination is still ongoing.

General description of adverse reactions in clinical trials of this product

A total of 14,572 subjects aged 18 and above were enrolled in a series of clinical trials conducted domestic and overseas, of which 7,658 subjects received at least one dose. All subjects have completed at least 28 days follow-up after full immunization, and long-term safety visits are ongoing.

According to the grading standard of adverse reaction incidence from Council for International Organizations of Medical Sciences (CIOMS), i.e. very common (≥10%), common (1%-10%, 1% was inclusive), uncommon (0.1%-1%, 0.1% was inclusive), rare (0.01%-0.1%, 0.01% was inclusive) and very rare (<0.01%), all adverse reactions were summarized and described as follows.

1. Adverse reactions at injection site

Very common: pain

Common: swelling, pruritus, erythema, induration

Uncommon: burn at injection site

2. Systemic adverse reactions

Very common: headache, fatigue

Common: myalgia, nausea, diarrhea, arthralgia, cough, chills, pruritus, loss of appetite, rhinorrhea, sore throat, nasal congestion, abdominal pain

Uncommon: vomit, hypersensitivity, abnormal skin and mucosa, fever, tremor, flushing, edema, dizziness, drowsiness

Rare: muscle spasms, eyelid edema, nose bleed/epistaxis, abdominal distension, constipation, hyposmia, ocular congestion, hot flashes, hiccup, conjunctival congestion

3. Severity of adverse reactions

The severity of adverse reactions observed in these clinical trials is mainly Grade 1 (mild), the incidence rate of adverse reactions for Grade 3 and the above was 1.31%.

Grade 3 and above adverse reactions includes pain at injection site, cough, fever, headache, sore throat, abdominal pain, dizziness and drowsiness.

4. Serious adverse event (SAE)

No serious adverse event related to vaccination was identified up to February 3, 2021.

For detailed information of adverse reactions among these clinical trials, please refer to the complete version of the leaflet.

【CONTRAINDICATIONS】

1. People with allergic history reaction to any component (active or inactive ingredients, or any material used in process) of the vaccine or similar vaccines;

2. Previous severe allergic reactions to the vaccine (eg, acute anaphylaxis, angioedema, dyspnea, etc.);

3. People with severe neurological conditions (eg, transverse myelitis, Guillain-Barré syndrome, demyelinating diseases, etc.);

4. Patients with uncontrolled severe chronic diseases;

5. Pregnant and lactating women.

【PRECAUTIONS】

1. Due to the insufficient data of protection persistence, necessary protective measures should be taken in line with the COVID-19 epidemic.

2. Due to the insufficient data of efficacy in people aged 60 and above. When use CoronaVac among people aged 60 and above by relevant institutions, the health status and exposure risk of people aged 60 and above shall be considered.

3. This vaccine is strictly prohibited for intravenous injection. There is no safety and efficacy data of

subcutaneous or intradermal injection.

4. Before use, check whether the packaging container, label, appearance and validity period meet the requirements or not. Do not use if there are cracks in the glass needle tube, spots, stains and scratches on the outer surface of the glass needle tube, label is not clear or more than the expiration date and abnormal appearance.

5. Avoid expose CoronaVac to the disinfectant during use.

6. This product should be stored at places out of reach of children.

7. Adequate treatment provisions, including epinephrine injection and emergency treatment, should be available for immediate use. Individuals should be observed for at least 30 minutes on site after vaccination.

8. Do not mix with other vaccines in the same syringe.

9. Do not freeze. It shall be administered immediately after open.

10. Patients with acute diseases, acute exacerbation of chronic diseases, severe chronic diseases, allergies and fever should be used with caution; if necessary, delay vaccination after doctor's evaluation.

11. Patients with diabetes and convulsions, epilepsy, encephalopathy or mental illness history or family history should be used with caution.

12. Patients with thrombocytopenia or hemorrhagic diseases, intramuscular injection of this product may cause bleeding, so it should be used with caution.

13. The safety and efficacy data of this product on people with impaired immune function (such as malignant tumor, nephrotic syndrome, AIDS patients) have not been obtained, and the vaccination of this product should be based on individual considerations.

14. The injection of human immunoglobulin should be given at least one month interval to avoid affecting the immune effect.

15. No clinical study has been carried out on the evaluation of immune response with other vaccines on

the immunogenicity at the same time (before, after or at the same time). Professionals should be consulted when concomitant use.

16. Do not use if there is any adverse reaction of nervous system after inoculation.

17. Like other vaccines, the protective effect may not reach 100% for all recipients.

【SPECIAL POPULATION MEDICATION】

1. Women of childbearing age: the data collected of women with unexpected pregnancy after vaccination from clinical trials are very limited, which is not enough to deicide the risk of adverse pregnancy outcomes after vaccination.

2. Pregnant or lactating women: the clinical data of pregnant and lactating women are not available at present.

3. People aged 60 and above: the immunogenicity and safety data from conducted clinical trials have been obtained, while the efficacy data from phase 3 clinical trial is insufficient.

【DRUG-DRUG INTERACTIONS】

1. Concomitant use with other vaccines: no clinical study has been carried out on the evaluation of immune response with other vaccines on the immunogenicity at the same time (before, after or at the same time).

2. Concomitant use with other drugs: immunosuppressive drugs, such as immunosuppressive drugs, chemotherapy drugs, antimetabolic drugs, alkylating agents, cytotoxic drugs, corticosteroid drugs, etc., may reduce the immune response to this product.

3. Patients undergoing treatment: for patients undergoing treatment, please consult the professional doctors before use CoronaVac to avoid possible drug interactions.

【STORAGE】

Store and transport between +2-8℃, and protect from light.

【SHELF LIFE】

The shelf life of the vaccine is tentatively scheduled as 12 months.

【PACKAGE】

Vial or pre-filled syringe. One vial or syringe per box.

【SPECIFICATION IMPLEMENTED】

YBS00152021

【AUTHORIZATION NO.】

【MARKETING AUTHORIZATION HOLDER】

Name: Sinovac Life Sciences Co., Ltd.

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