Approval Date:

Revision Date:

Recombinant COVID-19 (XBB) Trimer Protein Vaccine (Sf9 Cell)

Package Insert

Please read this instruction carefully and use under the guidance of a physician.

[NAME OF THE MEDICAL PRODUCT]

Generic Name: Recombinant COVID-19 (XBB) Trimer Protein Vaccine (Sf9 Cell)

Trade Name: Coviccine® XBB

English Name: Recombinant COVID-19 (XBB) Trimer Protein Vaccine (Sf9 Cell)

Chinese Phonetic Alphabet: Chongzu Xinguan Bingdu（XBB Bianyizhu）Sanjuti Danbai Yimiao (Sf9 Xibao)

[COMPOSITION]

This vaccine is produced by the spike receptor-binding domain (S-RBD) of the XBB.1.5 variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and heptad repeat (HR) trimeric fusion protein, which is expressed and secreted by using a recombinant baculovirus vector in Sf9 cells, followed by purification, and mixed with a squalene-based oil-in-water emulsion adjuvant in the appropriate proportions. The vaccine does not contain any preservatives or antibiotics.

Active Ingredients: Recombinant trimeric S-RBD-HR protein derived from XBB.1.5 variant of SARS-CoV-2.

Adjuvant: Squalene-based oil-in-water emulsion adjuvant.

Excipients: Disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride.

[DESCRIPTION]

This vaccine is a homogeneous milky-white liquid, with no visible foreign matter.

[TARGET GROUPS FOR VACCINATION]

Individuals aged 18 and above.

[THERAPEUTIC INDICATION]

This vaccine is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 variants.

[STRENGTH]

Each vial contains 0.5 mL, with a total of 60 μg of recombinant S-RBD-HR trimeric protein (2 doses for human use). A single human dose is 0.25 mL containing 30 μg of recombinant S-RBD-HR trimeric protein.

[ADMINISTRATION AND DOSAGE]

1. Primary series: This vaccine is to be administered as a series of 3 doses (30 μg, 0.25 mL per dose) 3-4 weeks apart.
2. Booster doses: A booster dose of 30 μg (0.25 mL) may be administrated at least 3 months after the last of ≥2 previous COVID-19 vaccine doses.
3. Or adhere to recommended schedule of the National Administration of Disease Control and Prevention.

4. Coviccine® XBB is for intramuscular injection only, preferably in the deltoid muscle of the upper arm. Shake well before injection.

[ADVERSE REACTIONS]

The safety data of this vaccine were obtained from a clinical trial conducted within China: a multi-center, randomized, double-blind, placebo-controlled Phase III clinical study evaluating the protective efficacy, safety and immunogenicity of Recombinant COVID-19 (XBB) Trimer Protein Vaccine (Sf9 Cell) in booster immunization to prevent SARS-CoV-2 infection in a population of 18 years and older, of which 40% were the elderly population (≥60 years of age). The trial collected the local and systemic solicited adverse events (AEs) from 0 to 7 days after booster vaccination and non-solicited AEs up to 30 days after vaccination in all subjects, and also monitored serious adverse events (SAEs) and adverse events of special interest (AESIs) up to 12 months after booster immunization.

1. General description of adverse reactions in the clinical trial

To date, a total of 4,802 subjects have been enrolled in the clinical trial, of which 3,151 subjects have received a booster dose of this vaccine, all of whom have completed at least 7 days of safety follow-up, with the long-term safety follow-up ongoing.

Adverse reactions were classified according to the frequency of adverse reactions recommended by the Council for International Organizations of Medical Sciences (CIOMS): very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), and very rare (<0.01%). Adverse reactions to this vaccine were described as per the CIOMS criteria as follows:

(1) Injection site adverse reactions

Very common: injection site pain.

Common: injection site erythema, injection site swelling, injection site induration.

(2) Systemic adverse reactions

Common: fever, fatigue.

(3) Severity of adverse reactions

The reported adverse reactions were mainly grade 1 and grade 2. The incidence of vaccine-related adverse reactions of grade 3 or above was 1.50%, with fever as the main symptom.

(4) Related serious adverse events (SAEs)

As of March 20, 2024, no vaccine-related serious adverse events have been reported.

2. Adverse reactions in the clinical trial

The clinical data available on safety indicate that this vaccine has a good safety profile.

Safety data from Phase III clinical trials:

The overall incidence of adverse reactions in subjects following vaccination was 15.11%, of which the incidence of local solicited adverse reactions was 14.00%, with symptoms mainly including: injection site pain (11.49%), injection site erythema(1.62%), injection site swelling (1.43%), and injection site induration (1.11%). The incidence of systemic adverse reactions was 3.65%, with symptoms mainly including: fever (1.62%), fatigue (1.21%), myalgia (0.92%), and arthralgia (0.48%). The solicited adverse reactions were mainly grade 1 (mild), with an incidence of 11.77%; grade 2 with an incidence of 1.30%; and grade 3 with an incidence of 0.35%. No solicited adverse reactions above grade 3 occurred.

The overall incidence of adverse reactions following vaccination in elderly (≥60 years) subjects was 10.68%, of which the incidence rate of local solicited adverse reactions was 7.55%, with symptoms

mainly including: injection site pain (7.40%), injection site erythema (0.99%), injection site swelling (0.53%), and injection site induration (0.31%). The incidence of systemic solicited adverse reactions was 2.29%, with symptoms mainly including: fever (0.99%), fatigue (0.61%), myalgia (0.38%), and arthralgia (0.23%). The solicited adverse reactions were mainly grade 1 (mild) with an incidence of 8.24%, grade 2 with an incidence of 0.84%, and grade 3 with an incidence of 0.15%. No adverse reactions of above grade 3 occurred, and no serious adverse reactions.

No vaccine-related serious adverse events occurred. There were no adverse reactions leading to withdrawal/ death.

[CONTRAINDICATIONS]

1. People with history of allergic reaction to any component, or any material used in the manufacturing process, or people who have developed allergic reaction to vaccines of the same type.
2. Previous severe allergic reactions (e.g., acute anaphylaxis, angioneurotic edema, dyspnea, etc.)
3. Patients with severe neurological disorders (e.g., transverse myelitis, Guillain-Barre Syndrome, demyelination disease, etc.).
4. Pregnant and breastfeeding women.

[WARNINGS AND PRECAUTIONS]

1. This vaccine is packaged in 2 doses with each vial containing enough vaccine for 2 individuals, each dose for human use is 0.25 mL. Use immediately after opening. The recommended practice is simultaneous vaccination of 2 individuals. In cases where simultaneous vaccinations are not possible, only a single dose should be drawn for the first vaccination, and the remaining vaccine should be kept in the vial and stored refrigerated at 2°C to 8°C, discard the vial after 8 hours. To ensure the uniformity of the vaccine content for the two doses, the vaccine vial should be shaken and mixed well before withdrawing the vaccine.
2. Check the packaging container, label, appearance and expiry date before use. Do not use it in case of any abnormal condition, including cracks in the vial, spots, stains, scratches on the outer surface, unclear label, expired product, or turbid product. Shake well before use. Do not use the vaccine if the vial shows abnormities such as foreign matters, or clumps that can't disappear after shaking.
3. Freezing is strictly prohibited.
4. Keep out of the reach of children.
5. Do not mix with other vaccine in the same syringe.
6. This vaccine must not be administered by intravascular injection. Safety and efficacy of this vaccine have not been assessed through subcutaneous and intradermal injection.
7. The recipients should be observed for at least 30 minutes on site after injection. Adrenaline and other necessary medications and monitoring equipment should be available for first aid in case of severe anaphylactic reactions.
8. A second dose should not be given to those who have experienced allergic reactions or other abnormal circumstances after the first dose.
9. Patients with diabetes, or history of convulsions, epilepsy, encephalopathy or mental illness, or family history of those diseases should be used with caution.
10. Patients with acute diseases, atopy and fever should be used with caution; if necessary, delay vaccination after doctor's evaluation.
11. Patients with thrombocytopenia or hemorrhagic diseases, intramuscular injection of this vaccine may cause bleeding, so it should be used with caution.
12. The injection of immunoglobulin should be given at least one month interval to avoid affecting the immune effect.
13. The safety and efficacy of this vaccine on immunocompromised individuals (such as patients with malignant tumors, nephrotic syndrome and HIV/AIDS) have not been assessed. Individualized

vaccination programs are recommended.

14. The duration of protection of this vaccine is temporarily unknown by ongoing clinical trials. Necessary protective measures are needed after vaccination.
15. Like other vaccines, vaccination with this vaccine may not protect all vaccine recipients.

[DRUG INTERACTIONS]

1. Concomitant administration: Clinical studies of the immunogenicity impact of co-administration (prior, concomitant, or subsequent) of this vaccine with other vaccines have not been conducted.
2. Concomitant use with other drugs: Drugs with immunosuppressive effects, including immunosuppressive drugs/agents, chemotherapy drugs, antimetabolites, alkylating agents, cytotoxic drugs, corticosteroids, etc., may lead to suppression of immune response to this vaccine.
3. Patients undergoing treatment: In order to avoid possible drug interactions in patients who are taking medication, it is recommended to ask a doctor before use.

[USE IN SPECIFIC POPULATIONS]

Data from clinical studies on the use of this vaccine in specific populations are not available, and there are no reliable references.

[CLINICAL STUDY]

1. Data on protective efficacy

The Phase III clinical study of this vaccine was conducted in a randomized, double-blind, placebo-controlled design in population aged 18 years and older and was used to assess the protective efficacy of this vaccine.

Protective efficacy 7 days after booster immunization with this vaccine

This vaccine was administered in booster immunization to prevent COVID-19 caused by SARS-CoV-2 variants, which showed a good protective efficacy 7 days after booster vaccination in adult population, elderly population and population with underlying health conditions, with an overall protective efficacy of 70.54%, and a two-sided 95% confidence interval of (55.45%, 80.52%).

Among them, the protective efficacy 7 days after booster vaccination in the adult population (18-59 years old) was 72.83%, with a two-sided 95% confidence interval of (53.56%, 84.10%); the protective efficacy 7 days after booster vaccination in the elderly population (≥60 years old) was 67.27%, with a two-sided 95% confidence interval of (37.19%, 82.94%); and 7 days after booster immunization with this vaccine, the protective efficacy against moderate/severe COVID-19 cases and COVID-19 cases causing hospitalization/death due to SARS-CoV-2 infection was 100.00%. An exploratory study was also conducted on the protective efficacy to prevent SARS-CoV-2 infection, which suggests that this vaccine has a good protective efficacy to prevent SARS-CoV-2 infection 7 days after booster vaccination, with a protective efficacy of 69.69%.

Protective efficacy 14 days after booster immunization with this vaccine

This vaccine was administered in booster immunization to prevent COVID-19 caused by SARS-CoV-2 variants, which showed a good protective efficacy 14 days after booster vaccination in adult population, elderly population and population with underlying health conditions, with an overall protective efficacy of 70.08%, and a two-sided 95% confidence interval of (54.70%, 80.24%).

Among them, the protective efficacy 14 days after booster vaccination in the adult population (18-59 years old) was 72.83%, with a two-sided 95% confidence interval of (53.56%, 84.10%); the protective efficacy 14 days after booster vaccination in the elderly population (≥60 years old) was 65.85%, with a two-sided 95% confidence interval of (34.09%, 82.31%); in the population combining the population with underlying health conditions and the immunocompromised population, the protective efficacy 14 days after booster vaccination was 80.77%, with a two-sided 95% confidence interval of (55.86%, 91.62%).

And 14 days after booster immunization with this vaccine, the protective efficacy against moderate/severe COVID-19 cases and COVID-19 cases causing hospitalization/death due to SARS-CoV-2 infection was 100.00%. An exploratory study was also conducted on the protective efficacy to prevent SARS-CoV-2 infection, which suggests that this vaccine has a good protective efficacy to prevent SARS-CoV-2 infection 14 days after booster vaccination, with a protective efficacy of 69.22%.

In this clinical trial, the viral gene sequences of COVID-19 cases occurred were mainly SARS-CoV-2 Omicron JN.1 and its sub-variants, which accounted for 97.73%. The data suggests that this vaccine has good broad-spectrum protective efficacy against symptomatic COVID-19 caused by infection with JN.1 and its sub-variants.

2. Data on immunogenicity

The immunogenicity data of this vaccine was obtained from the Phase III clinical trial, which showed that a high level of humoral and cellular immunity could be stimulated after one dose of this vaccine was administered to the subjects.

High levels of neutralizing antibodies against JN.1 variant and XBB.1.5 variant were produced after vaccination. On Day14 and Day30 after vaccination, the geometric mean titers (GMT) of the neutralizing antibodies against JN.1 variant euvirus were 1094.06 and 1035.40, which were 52.97 and 49.81 times higher than those before vaccination, and the positive seroconversion rates were 97.95% and 93.29%. On Day7, Day14 and Day30 after vaccination, the neutralizing antibody GMTs against JN.1 variant pseudovirus were 3130.16, 3968.23 and 3510.23, which were 15.83, 19.56 and 17.55 times higher than those before vaccination, and the positive seroconversion rates were 79.59%, 81.51% and 83.89%; the neutralizing antibody GMTs against XBB.1.5 variant pseudovirus were 1497.79, 3970.62 and 3749.79, which were 5.84, 15.33 and 14.68 times higher than those before vaccination, and the positive seroconversion rates were 55.78%, 82.19% and 81.21%.

On Day14 and Day30 after vaccination, the neutralizing antibody GMTs against XBB.1.16 variant euvirus were 2235.20 and 2094.79, which were 20.66 and 19.17 times higher than those before vaccination, and the positive seroconversion rates were 82.19% and 84.56%; the neutralizing antibody GMTs against Delta variant euvirus were 368.50 and 616.02, which were 9.83 and 9.03 times higher than those before vaccination, and the positive seroconversion rates were 73.97% and 67.81%. On Day7, Day14 and Day30 days after vaccination, the neutralizing antibody GMTs against XBB.1.16 variant pseudovirus were 1945.74, 3632.26 and 4832.52, which were 12.07, 21.82 and 29.69 times higher than those before vaccination, and the positive seroconversion rates were 78.23%, 90.41% and 95.30%; the neutralizing antibody GMTs against the Delta variant pseudovirus were 1917.45, 3838.31 and 6293.81, which were 6.71, 13.46 and 21.89 times higher than those before vaccination, and the positive seroconversion rates were 63.27%, 82.19% and 91.28%.

After administration with this vaccine, high levels of specific IgG antibodies against the SARS-CoV-2 S-RBD protein could be produced in subjects. On Day7, Day14 and Day30 after vaccination, the specific IgG antibody GMTs against SARS-CoV-2 S-RBD protein were 15644.10, 29945.67 and 22103.40, which were 6.87, 13.08 and 9.64 times higher than those before vaccination, and the positive seroconversion rates were 65.99%, 87.67% and 81.21%.

This vaccine has good immune persistence, high levels of specific IgG antibodies were sustained 3 months after vaccination. Data on neutralizing antibodies 3 months after vaccination and data on immunogenicity 6 month after vaccination are being collected. The specific IgG antibody GMT against SARS-CoV-2 S-RBD protein 3 months after vaccination was 12681.13, 5.54 times higher than that before vaccination, with a positive seroconversion rate of 61.49%.

The clinical trial data showed that this vaccine could induce strong specific cellular immune response in human body. The positive rate of IFN-γ secreted by T cells specifically stimulated by SARS-CoV-2 S-RBD protein was 50.00% before vaccination and 83.33% on Day14 after inoculation; interleukin-2

(IL-2) positive rate was 60.00% before vaccination and 96.67% on Day14 after vaccination; interleukin-4 (IL-4) positive rate was 20.00% before vaccination and 53.33% on Day14 after vaccination.

[STORAGE]

Store and transport refrigerated at 2°C to 8°C. Protect vials from light. Do not freeze. Discard if the vaccine has been frozen.

This vaccine is a two-dose human vaccine. After the first dose is used, if immediate administration is not possible, the remaining vaccine in the vial should be stored at 2~8℃ for no more than 8 hours. Discard vial after 8 hours.

[PACKAGE]

Packaged in injection vials made of middle borosilicate glass tubing, and covered with a bromobutyl rubber stopper for injection (brominated), which does not contain natural latex. 0.5 mL/vial, 1 vial/box.

[SHELF-LIFE]

24 months tentatively.

[SPECIFICATION IMPLEMENTED]

Manufacturing and Testing Procedures for Recombinant COVID-19 (XBB) Trimer Protein Vaccine (Sf9 Cell).

[AUTHORIZATION NUMBER]

To be determined.

[MARKETING AUTHORIZATION HOLDER]

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