COVID-19 Vaccine Explainer

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World Health Organization

COVID-19 Vaccine (Whole Virion Inactivated Corona Virus vaccine), BBV152, COVAXIN®

EUL holder: Bharat Biotech International Limited

The COVID-19 Vaccine COVAXIN® (BBV152) is a whole virion inactivated SARS-CoV-2 based vaccine against coronavirus disease 2019 (COVID-19). It stimulates the body's immune system without risk of causing disease: once inactivated viruses get presented to the body's immune system, they stimulate the production of antibodies and make the body ready to respond to an infection with live SARS-CoV-2. This vaccine contains aluminum-based adjuvant to enhance the response of the immune system, and the preservative 2-phenoxyethanol to secure microbial stability of the vaccine.

A large Phase 3 trial in individuals aged 18 years and above has shown that two doses administered at an interval of 4 weeks had the efficacy of 78% against COVID-19 of any severity and 93% against severe COVID-19 14 days or more after the second dose. In adults aged <60 years, vaccine efficacy was 79%, and in those aged ≥60 years it was 68%. Vaccine efficacy against asymptomatic SARS-CoV-2 infection was 64%. The median duration of follow up available at the time of review was 99 days.

The data reviewed at this time support the conclusion that the known and potential benefits of COVAXIN® outweigh the risks that are known or considered possible, and WHO recommends the use of COVAXIN® in individuals aged ≥18 years.

Date of WHO Emergency Use Listing (EUL) recommendation: 3 November 2021

Date of prequalification (PQ): not applicable

National regulatory authorities (NRAs) can use reliance approaches for in-country authorization of vaccines based on WHO PQ/EUL or emergency use authorizations by stringent regulatory authorities (SRAs).

Product characteristics

Presentation	Fully liquid, inactivated, adjuvanted and preserved suspension in vials
Number of doses	1, 5, 10 and 20 (one dose 0.5 mL)
Vaccine syringe type and needle size	Auto-disable (AD) syringes: 0.5 mL Needles for intramuscular injection 23G × 1" (0.60 × 25 mm)

[1] Contents will be updated as new information becomes available.

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Schedule and administration

Recommended for age	18 years of age and above
Recommended schedule	2 doses (0.5 mL each) at a recommended interval of 4 weeks: Dose 1: at the start date Dose 2: 28 days after first dose. If the second dose is inadvertently administered earlier than 4 weeks after the first, the dose does not need to be repeated. If the second dose is inadvertently delayed beyond 4 weeks, it should be given at the earliest possible opportunity. It is recommended that all vaccinated individuals receive two doses. According to current recommendation, the same product should be used for both doses. If different COVID-19 vaccine products are inadvertently administered in the 2 doses, no additional dose of either vaccine is recommended at this time. Additional dose of a vaccine may be needed as part of an extended primary series for immunocompromised and other populations where the immune response after standard primary series is deemed likely to be insufficient. The need for and timing of boosters is being assessed.
Route and site of administration	Intramuscular (i.m.) administration The preferred site is deltoid muscle.
Dosage	0.5 mL (single dose)
Diluent	None needed
Mixing syringe	None needed
Preparation/ reconstitution/ dilution requirement	**No dilution is required.** **Vaccine administration:** 1. Vaccine is ready to use, do not dilute. 2. Shake the vial well, to obtain a uniform, whitish translucent suspension. 3. Visually inspect to ensure no particulate matter or other coloration is present in the vial. If visible particles or discoloration are present, discard the vial. 4. Record date and time of the first use (first puncture and withdrawal of the dose) on the vial label when using multi-dose vials. 5. Draw up the vaccine from the vial at the time of administration, pre-loading of syringes is not recommended. 6. Preferably, use all vaccine in the vial immediately or within 6 hours after first puncture. During vaccination session, keep between +2 and +8 °C and protected from light. Keep opened vaccine vial in the foam pad of the vaccine carrier. If any liquid remains in the multi-dose vaccine vial after withdrawing the final dose, discard the vial and do not combine residual vaccine from multiple vials.
Multi-dose vial policy	Discard any unused vaccine 6 hours after first puncture or at the end of the immunization session, whichever comes first.[2]

[2] Since this vaccine contains preservative, in settings where temperature control is not an issue, the vaccine can be kept and used for up to 28 days (4 weeks) after first puncture if the appropriate handling procedures were followed (i.e. vial was kept between +2 and +8 °C and expiration date is legible and not passed) in accordance with WHO Multi-dose Vial Policy Statement WHO/IVB 14.07.

However, the expiry date must be updated before the open vial is returned to the refrigerator after the immunization session in which the vial is first punctured as follows:

- If 28-day (4 weeks) period is within the original expiry date printed on the label, cross it out to mark as not valid. Write down the new expiry date which would be 28 days (4 weeks) from the date you first punctured the vaccine vial.
- If 28-day (4 weeks) period is longer than the original expiry date printed on the label, respect the original expiry date.

Schedule and administration contd.

Contraindications	• Known history of anaphylaxis to any component of the vaccine. • Persons who developed anaphylaxis after the first dose should not receive a second dose of the COVAXIN® vaccine.
Precautions	• All persons should be vaccinated by a health-care professional in settings where appropriate medical treatment is available in case of allergic reactions. An observation period of 15 minutes after vaccination should be ensured. • For persons with a history of anaphylaxis to any other vaccine or injectable therapy, regardless of route of administration, a risk assessment should be conducted by a health professional. Such individuals should be observed 30 minutes after vaccination in a health-care setting where anaphylaxis can be immediately treated. • Vaccination of people suffering from acute severe febrile illness (body temperature over 38.5 °C) should be postponed until they are afebrile. • Vaccination of persons with acute COVID-19 should be postponed until they have recovered from acute illness and criteria for discontinuation of isolation have been met.
Special population groups (based on available data as of 5 October 2021)	For persons with **comorbidities**, phase 3 clinical trial demonstrated that the vaccine has only slightly reduced efficacy profile in persons with cardiovascular disease, respiratory disease, diabetes, liver disease, and obesity. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19 and death. **Persons aged 60 years or more** made up only 11% of participants of the phase 3 trial; the vaccine showed 68% efficacy against COVID-19 of any severity and an acceptable safety profile for this age group. Post-introduction effectiveness studies are not yet available but are anticipated. Use of vaccine in persons aged ≥60 years is recommended. Available data on administration in **pregnant women** are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. Studies in pregnant women are planned, including a pregnancy sub-study and a pregnancy registry. The only safety data specific to COVAXIN® adjuvant which has not been used in other licensed vaccines, come from the COVAXIN® safety profile which does not include data on pregnant women. However, over 120 000 pregnant women from India received this vaccine and minor adverse events were found, but data on neonatal outcomes have not yet been collected. On the basis of previous experience with other inactivated vaccines, it is expected that the vaccine effectiveness in pregnant women will be similar to that observed in non-pregnant women of similar age. Given that COVID-19 has increased risk of severe outcomes in pregnant women, WHO recommends the use of COVAXIN® in pregnant women if the benefits of vaccination outweigh the potential risks. To help pregnant women make this assessment, they should be provided with information about the risks of COVID-19 in pregnancy (including, for example, that some pregnant women are at increased risk of infection, or have comorbidities that add to their risk of severe disease), the likely benefits of vaccination in the current epidemiological context, and the current limitations of the safety data in pregnant women. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Schedule and administration contd.

Special population groups (continued)	There are no data on potential benefits or risks of COVAXIN® to **breastfed children**. As this is not a live virus vaccine, it is unlikely to pose a risk to the breastfed child. Vaccine effectiveness is expected to be similar in lactating women as in other adults. WHO does not recommend discontinuing breastfeeding because of vaccination. Data on the safety and immunogenicity of 2 doses of COVAXIN® in **persons living with HIV** who are stable on antiretroviral therapy are insufficient to allow assessment. It is possible that their immune response to the vaccine may be reduced. Such persons who are a part of a group recommended for vaccination may be vaccinated, given that the vaccine is non-replicating. Where possible, information and counselling should be provided to inform individuals on the potential benefits and risks. Testing for HIV infection prior to vaccine administration is not necessary. Available data for WHO EUL COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity are lower in **moderately and severely immunocompromised persons (ICP)** (i.e. transplant recipients, persons with active cancer, immunodeficiency, on active treatment with immunosupressives, and persons living with HIV with CD4 cell count of <200 cells/µL) than in persons without immunocompromising conditions. Based on the emerging evidence and significant risk of severe COVID-19 for ICPs if infected, WHO recommends an extended primary series including the third dose, to be given at least 1 month and within 3 months after dose 2, in order to increase protection as quickly as possible in this population group. If more than 3 months have elapsed since dose 2, the third dose should be given at the earliest opportunity or as discussed with the treating physician. Information and, where possible, counselling about the limitations surrounding data on administration of an additional dose to ICPs should be provided to inform individual benefit–risk assessment. For persons who have received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment, vaccination should be deferred for at least 90 days to avoid interference of treatment with vaccine-induced immune response as a precautionary measure. Persons in special settings such as refugee and detention camps, prisons, slums and other settings with high population densities where physical distancing is not implementable, should be prioritized for vaccination, taking into account national epidemiological data, vaccine supply and other relevant considerations.

Stability and storage

Vaccine storage temperature	Store in the original packaging in a refrigerator at +2 to +8 °C. **Do not store in a freezer.**
Shelf life at different temperatures[3]	**Unopened vials in a refrigerator** between +2 and +8 °C: 9 months or until expiry date stated on the label.
Freeze sensitivity	Do not freeze.
Light sensitivity	Store in the original packaging to protect from light. Avoid exposure to direct sunlight and ultraviolet light.
Conditions before use	Vaccine is ready to use; it may be used if kept cooled at +2 °C to +8 °C.
Wastage rates	Will be dependent on country context.
Buffer stock needed	Will be dependent on country context.

[3] In accordance with WHO Multi-dose Vial Policy Statement WHO/IVB 14.07, in settings where temperature control is not an issue, punctured vials can be kept in a refrigerator between +2 and +8 °C until the updated expiry date.

Labelling and packaging

Vaccine Vial Monitor (VVM)	Not included
Information on vial label	Name and type of vaccine, method of administration, dosage, storage temperature, manufacturing and expiry date, batch number
Information on secondary packaging	Name of vaccine, pharmaceutical form, method of administration, dosage, composition (active substance and excipients), manufacturing date, batch number, authorisation number, name and address of manufacturer
Information on tertiary packaging	Type of vaccine, name of manufacturer, presentation, batch number, date of expiry, quantity and storage conditions
Secondary packaging dimension and volume per dose	**Single-dose vials:** Multipack holding 36 vials (36 doses); 11 × 11 × 4.3 cm Volume per dose: 14.45 cm^3 **5-dose vials:** Multipack holding 36 vials (180 doses); 11 × 11 × 4.3 cm Volume per dose: 2.89 cm^3 **10-dose vials:** Multipack holding 16 vials (160 doses); 10 × 10 × 4.3 cm Volume per dose: 2.69 cm^3 **20-dose vials:** Multipack holding 16 vials (320 doses); 10 × 10 × 5.5 cm Volume per dose: 1.72 cm^3
Tertiary packaging dimension (corrugated box contained within insulated box)	**Single-dose vials:** Inner corrugated box containing 32 secondary multipacks with a total of 1152 vials (1152 doses): 47.5 × 24 × 18.5 cm Insulated box: 65 × 52 × 42 cm ± 0.5 cm **5-dose vials:** Inner corrugated box containing 32 secondary multipacks with a total of 1152 vials (36 864 doses): 47.5 × 24 × 18.5 cm Insulated box: 65 × 52 × 42 cm ± 0.5 cm **10-dose vials:** Inner corrugated box containing 32 secondary multipacks with a total of 512 vials (5120 doses): 41 × 20 × 19 cm Insulated box: 57.5 × 46 × 37 cm ± 0.5 cm Inner corrugated box containing 18 secondary multipacks with a total of 288 vials (2880 doses): 31 × 21 × 15.5 cm Insulated box: 57.5 × 46 × 37 mm ± 0.5 cm **20-dose vials:** Inner corrugated box containing 24 secondary multipacks with a total of 384 vials (7680 doses): 41 × 20 × 19 cm Insulated box: 57.5 × 46 × 37 cm ± 0.5 cm

Safety information*

Possible events (by frequency)	Observed events were mostly mild and short lived. **Local events:** observed more frequently after the first dose **Very common (≥1/10):** Pain at the injection site **Uncommon (≥1/1000 to <1/100):** Redness, swelling, induration at the injection site **Systemic events:** observed more frequently after the second dose **Common (≥1/100 to <1/10):** Fever, fatigue, headache, myalgia, cough, oropharyngeal pain **Not known (cannot be estimated from available data):** Anaphylaxis, hypersensitivity
Co-administration of vaccines/medicines	There should be a minimum interval of 14 days between administration of this and any other vaccine against other diseases, until data on co-administration become available.

*From clinical trials

Important reminders

Vaccination session and vaccine administration

Before, during, and after vaccination, all people should continue to follow current guidance for protection from COVID-19 in their area (e.g. wearing a mask, keeping physical distance, hand hygiene, appropriate ventilation). Close contacts of immunocompromised people, particularly caregivers, should be vaccinated if eligible, and additional public health and, depending on local epidemic circumstances, social measures at the household level are warranted.

Vaccination should be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. Viral or serological testing is not recommended for the purpose of decision-making about vaccination. Based on current data, symptomatic reinfection is uncommon within 6 months after an initial natural infection, and in the context of limited vaccine supply, persons with PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may choose to delay vaccination until near the end of this period. However, emerging data indicate that symptomatic reinfection may occur in settings where variants with evidence of immune escape are circulating, and in these settings, earlier vaccination after infection may be advisable (e.g. 3 months after natural infection). The length of this time period may be revised when more data on duration of immunity after natural infection become available.

The presence of a minor infection such as a cold or low-grade fever should not delay vaccination.

A person with acute PCR-confirmed COVID-19 should not be vaccinated until after they have recovered from acute illness and the criteria for discontinuation of isolation have been met. The optimal minimum interval between a natural infection and vaccination is not yet known.

Any vaccine unused before the expiry date or waste material should be disposed of in accordance with local requirements. If content of a vial leaks out, spills should be disinfected with an appropriate antiviral disinfectant.

Encourage a vaccine recipient to complete the vaccination series to optimize protection and schedule the time for the second dose. The same vaccine product should be used for both doses. When scheduling vaccination for occupational groups (e.g. health workers) consideration should be given to the reactogenicity profile observed in clinical trials, occasionally leading to time off work in the 24–48 hours following vaccination.

Government advice on public health and social measures should continue to be followed by both vaccinated and unvaccinated individuals. Country strategies related to COVID-19 control should be designed to minimize disruption to children's participation in education and other aspects of social life.

SARS-CoV-2 variants

As SARS-CoV-2 viruses undergo evolution, new variants may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition. Data from the phase 3 clinical trial included individuals infected with variants of concern such as Alpha, Delta and Kappa. Numbers were too low for vaccine efficacy estimates for Alpha. Vaccine efficacy against all variant-related COVID-19 disease was 71% (95% CI: 50–84) with an efficacy of 90% (95% CI: 30–100) against Kappa, and 65% (95% CI: 33–83) against Delta. WHO currently recommends the use of COVAXIN® even if the variants are present in the country. There is an urgent need for a coordinated approach for surveillance and evaluation of variants and their potential impact on vaccine effectiveness. Countries using the vaccine in the presence of variants are encouraged to monitor vaccine effectiveness and study eventual breakthrough infections due to variants.

SARS-CoV-2 tests

COVAXIN® contains inactivated SARS-CoV-2 virus which elicits immunological response to the spike and nucleocapsid protein. As currently available antibody tests for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein, a positive test could indicate either prior infection or prior vaccination. However, prior receipt of COVAXIN® will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests for diagnosis of acute/current SARS-CoV-2 infection. Antibody testing is not currently recommended to assess immunity to COVID-19 following COVAXIN® vaccination.

Resources and more information at:

https://extranet.who.int/pqweb/vaccines/who-recommendation-bharat-biotech-international-ltd-covid-19-vaccine-whole-virion

https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin

https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin-background