| World Health Organization | REGULATION AND PREQUALIFICATION DEPARTMENT |
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| | Vaccines & Immunization Devices Team (VAX) |

# WHO PUBLIC ASSESSMENT REPORT (WHOPAR)

**COVOVAX™**

**SARS-CoV-2 rS Protein Nanoparticle Vaccine (recombinant, adjuvanted)**

**Serum Institute of India Pvt. Ltd., India**


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## What is COVOVAX™?

**COVOVAX™** is a vaccine for preventing coronavirus disease (COVID-19) in people aged 12 years and older. The recommended COVOVAX™ contains a version of a protein found on the surface of SARS-CoV-2 (the virus that causes COVID-19).

COVOVAX™ has been adapted to target the most recent strains of the virus. This helps maintain protection against COVID-19. In this case COVOVAX™ contains a version of the protein from the Omicron XBB.1.5 subvariant of SARS-CoV-2.

COVOVAX™ is a dispersion for injection presented in a single dose vial (2R USP Type 1). The vaccine is adjuvanted. The dispersion is ready to use after a gentle agitation.

Each dose of vaccine (0.5 mL) contains:

| **Active components and quantity per dose** | |
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| SARS-CoV-2 spike protein (recombinant) | 5 µg |
| **Adjuvant** | |
| Matrix-M | 50 µg |
| **Excipients** | |
| Active component and adjuvant are co-formulated with formulation buffer (containing Disodium hydrogen phosphate heptahydrate, Sodium dihydrogen phosphate monohydrate, Sodium chloride and Polysorbate 80). | |

COVOVAX™ (XBB 1.5) will be available for the UN purchase in a carton box containing 50 vials. Each vaccine vial consists of 1 dose of 0.5 mL of vaccine. The vaccine should be administered by intramuscular injection only, preferably in the deltoid muscle of upper arm.

The vaccine is filled in a 2R USP Type 1 glass siliconized vial. The vial closure system is complemented with a bromo butyl rubber stopper with aluminum – flip off seal of blue pantone colored.

The stability data submitted by the prequalification holder supports a shelf life of 9 months when the vaccine is stored between 2°C to 8°C. The vaccine should be shipped and stored at this recommended temperature, and it should not be frozen. The current thermostability profile of the vaccine is best matched to a current WHO-approved VVM type VVM2. However, at the time of issuing the recommendation, the PQ holder is pursuing a better solution. To comply with this programmatic characteristic.

COVOVAX™ is manufactured by Serum Institute of India Pvt Ltd. having its registered office at 212/2, Off Soli Poonawalla Road, Hadapsar, Pune 411028, India.

## What is COVOVAX™ used for?

Data have shown that COVOVAX and its adapted vaccines cause the production of antibodies against SARS-CoV-2, to provide protection against COVID-19. The immune response to the vaccine is similar in adolescents and adults.

COVOVAX™ (**XBB 1.5**) is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations.

COVOVAX™ was originally given an "emergency use" recommendation (EUL) because there was more evidence to come about the vaccine. The PQ holder has provided comprehensive information, including data on the pharmaceutical quality of the vaccine. As a result, the EUL status has been switched to a standard prequalification.

## How is COVOVAX™ used?

COVOVAX™ is given in accordance with official recommendations issued at national level by public health bodies.

COVOVAX™ (XBB.1.5) is administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, COVOVAX™ (XBB.1.5) should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to people with a severely weakened immune system.
For more information about using COVOVAX™ (XBB.1.5), including information about the adapted vaccines, see the package leaflet or consult a healthcare professional.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an adverse reaction (e.g., anaphylactic reaction) following the administration of the vaccine.

## What are the vaccine characteristics?

COVOVAX™ (XBB.1.5) is a dispersion for injection, it is colourless to slightly yellow, clear to mildly opalescent.

COVOVAX™ (XBB.1.5) must be stored as recommended by manufacturer, between 2°C to 8°C. Under this recommended storage condition, the vaccine is stable for 9 months from the date of manufacture.

The vaccine does not contain preservative.

Cold chain volume per dose is 15.82 $cm^3$/dose in the 50 vials primary carton or secondary packaging.

## Who is the regulatory authority responsible for its oversight vis a vis WHO?

COVOVAX™ (XBB.1.5) is under the regulatory oversight of the Central Drugs Standard Control Organization (CDSCO) and the Drug Controller General of India (DCGI) under the Directorate General of Health Services, of the Ministry of Health & Family Welfare, Government of India. This is the regulatory agency of record for this vaccine.

**How has COVOVAX™ (XBB.1.5) been studied from the clinical point of view?**

The immunogenicity of the vaccine was evaluated in following clinical trials. Immunogenicity assessments comprised serum anti-S protein binding IgG, angiotensin converting enzyme 2 (ACE2) receptor binding inhibition, neutralizing antibodies, and cell-mediated immunity (CMI) by intracellular cytokine staining (ICCS).

**Study 2019nCoV-101,** a phase 1, first-in-human, randomized, observer-blinded, placebo-controlled trial evaluating the safety and immunogenicity of 5 μg and 25 μg SARS-CoV-2 rS with or without 50 μg Matrix-M1 adjuvant, administered 21 days apart on Days 0 and 21 as a bedside mixture, was done at two sites in Australia in healthy adult participants between ages18 and 59 years of age who were seronegative to SARS-CoV-2 at baseline. 134 participants were enrolled in part 1 and 1,288 participants enrolled in part 2.

**Study 2019nCoV-501** is a Phase 2a/b, randomized, observer-blinded, placebo-controlled trial evaluating the efficacy, safety and immunogenicity of NVX-CoV2373, administered 21 days apart on Days 0 and 21 as a coformulation, in healthy adult HIV-negative participants 18 to 84 years of age and medically stable adult HIV-positive participants 18 to 64 years of age who were seronegative to SARS-CoV-2 at baseline. A total of 4,419 participants were randomized.

**Study 2019nCoV-302** is a Phase 3, randomized, observer-blinded, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity of NVX-CoV2373, administered 21 days apart on Days 0 and 21 as a coformulation, in healthy and medically stable adult participants 18 to 84 years of age who were seronegative to SARS-CoV-2 at baseline. This study includes a Seasonal Influenza Vaccine Substudy, where approximately 400 participants received an additional IM injection of a licensed seasonal influenza vaccine on Day 0 in the opposite deltoid. A total of 15,187 participants were randomized (1:1) into Study 2019nCoV-302, with 15,139 receiving at least 1 dose of study vaccine (n = 7,569) or placebo (n = 7,570) and 14,930 receiving both doses of study vaccine (n = 7,467) or placebo (n = 7,463).

**Study 2019nCoV-301**, a phase 3, randomized, observer-blinded, placebo-controlled trial evaluating the efficacy, safety and immunogenicity of NVX-CoV2373, administered 21 days apart on Days 0 and 21 as a coformulation, in adult participants ≥ 18 years with a pediatric expansion in adolescents (12 to < 18 Years) is ongoing at multiple study sites in the US and Mexico. A total of 29,949 participants were randomized, out of which 19,965 were in the NVX-CoV2373 group and 9,984 were in the placebo group.

**A phase 2/3**, observer-blind, randomized, controlled study to determine the safety and immunogenicity of COVOVAX [SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M1™ adjuvant] in Indian adults aged ⩾18 years and children aged 2 to 17 years was done in India. There are 2 cohorts in this study. Adult cohort of 1600 individuals ⩾ 18 years of age and Pediatric cohort of 920 children of ⩾ 2 years of age. Of these, 460 children are of ≥ 12 to 17 years of age and 460 children are of ≥ 2 to 11 years of age.

**A phase 3**, observer-blind, randomized, controlled study to evaluate the safety and immunogenicity of a booster dose of Covovax in Indian adults who had received primary vaccination against COVID-19 at least 6 months ago (180 days from second dose of Covishield or Covaxin) is also ongoing in India. A total of 190 participants were enrolled (screened) and 187 were randomized in Covishield prime cohort).

*Summary of immunogenicity:* Phase I study in Australia, phase II study in Australia and USA, a Phase 2a/b study in South Africa, and Phase 3 studies in the United Kingdom and USA and Mexico analyses indicates that two-dose regimen of the vaccine induced high immune responses, with high titers of anti- spike IgG antibodies, with levels of neutralizing antibodies that closely correlated with anti- spike IgG. Also, vaccinated groups demonstrated higher level of protection against symptomatic COVID-19. The Phase 2/3 study in India showed that two-dose regimen of the vaccine showed that COVOVAX is noninferior to Novavax vaccine and induced high immune responses, with high titers of anti- spike IgG antibodies and more than 92% seroconversion to anti-S IgG at 14 days after the second dose. Antibody titers declined at 6 months (final study visit) which has already been observed in the Novavax studies as well as with other COVID-19 vaccines.

Booster administration of 5 μg SARS-CoV-2 rS with 50 μg Matrix-M adjuvant 6 months following a two-dose priming vaccination series on Days 0 and 21 induced robust immune responses 28 days after booster vaccination (Day 217) in healthy adult participants 18 to 84 years of age.

In children, a two-dose regimen of NVX-CoV2373, administered 21 (+7 days) days apart, markedly increased serum IgG antibody, hACE2 receptor binding inhibition antibody, and neutralizing antibody levels relative to placebo 2 weeks following second vaccination.

***Overview of Efficacy:*** Across the Phase 2a/b and two pivotal Phase 3 efficacy studies, a two-dose regimen of NVX CoV2373 (5 μg SARS-CoV-2 rS with 50 μg Matrix-M adjuvant), administered at least 21 days (+ 7 days) apart, met the prespecified study success criterion of their respective studies versus placebo in preventing PCR confirmed symptomatic mild, moderate, or severe COVID 19 with onset from at least 7 days after second vaccination (e.g. Day 28) in serologically negative (to SARS CoV-2) adult participants ⩾ 18 years of age. This includes data from two pivotal Phase 3 efficacy trials independently demonstrating ~90% efficacy against COVID-19 with a lower bound confidence interval (LBCI) > 30%, as well as 100% efficacy against severe disease.

***For pediatric expansion in adolescents (12 to < 18 Years):*** In pediatric expansion cohort of Clinical Study 2019nCoV-301 in the US, the primary efficacy endpoint was achieved with a VE of 79.54% (95% CI: 46.83, 92.13), during a period in which B.1.617.2 (Delta) was predominant in the country.

**Study 2019nCoV-313 (Omicron XBB.1.5):** A 2-Part Phase 2/3 Open-Label Study to Evaluate the Safety and Immunogenicity of an XBB.1.5 (Omicron Subvariant) SARS-CoV-2 rS Vaccine Booster Dose in Previously mRNA COVID-19 Vaccinated and Baseline SARS-CoV-2 Seropositive COVID-19 Vaccine Naïve Participants. The co-primary objectives in Part 1 were 1) to determine if NVX-CoV2601 booster induced superior antibody responses to the Omicron XBB.1.5 subvariant compared to the antibody responses of a historical control of NVX-CoV2373 and 2) to determine if NVX-CoV2601 booster induced non-inferior seroresponse rates (SRRs) compared to SRRs of a historical control of NVX-CoV2373 in participants who previously received ≥ 3 mRNA COVID-19 vaccinations.

The co-primary endpoints of the study were achieved as the Omicron XBB.1.5 subvariant vaccine NVX-CoV2601 induced a superior response in adjusted GMTs (ID50) against the Omicron XBB.1.5 subvariant virus along with a non-inferior SRR versus the historical control prototype Novavax vaccine NVX-CoV2373 at Day 28 following booster administration in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech COVID-19 mRNA vaccines.

***Safety summary:*** COVOVAX™ (XBB 1.5) is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The vaccine is well tolerated with an acceptable safety profile in adult and children.

**Other information about evaluation of COVOVAX™ (XBB.1.5)**

The transit from EUL to a standard prequalification is based on a vaccine prequalification dossier submitted in compliance with the CTD format.

The evaluation of COVOVAX™ (XBB.1.5) prequalification application was based on the review of the information submitted to WHO by Serum Institute of India Pvt Ltd. having its registered office at 212/2, Off Soli Poonawalla Road, Hadapsar, Pune 411028, India. .

The recommendation of this vaccine is based on the review of the information submitted to WHO by SIIPL, which included certifications (e.g., European Union Good Manufacturing Practices certificates), assessment reports and ultimately the license issued by the Drug Controller General of India (DCGI), which is the agency of record for the regulatory oversight of this vaccine.

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