Central Drugs Standard Control Organization
Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India
FDA Bhavan, ITO, Kotla Road, New Delhi -110002

Annexure - VIII

SUMMARY OF TECHNICAL EVALUATION REPORT

(PUBLIC ASSESSMENT REPORT)

SARS-CoV-2 (Covid-19) Vaccine containing Receptor Binding Domain of SARS-CoV-2 (CORBEVAX®)

M/s Biological E. Limited

1. **Generic Name:**
   SARS-CoV-2 (Covid-19) Strain- RBD203-N1 XBB.1.5

2. **Description& Dosage Form:**
   BE's SARS-CoV-2 (Covid-19) Vaccine (2CORBEVAX®) is a white turbid suspension with visible mineral carrier for intramuscular injection. Each dose is formulated with 25 µg of RBD antigen of SARS-CoV-2 (Covid-19) (Strain RBD-XBB.1.5), Buffer (Tris and NaCl in WFI) added with Aluminium Hydroxide gel and CpG 1018 as Adjuvant. No preservative is used in the formulation.

3. **Presentations approved:**
   Single dose vial of 0.5 mL (USP Type-I Glass vials).

4. **Composition (components and its quantity per dose):**
   Each dose of 0.5 mL Contains:

Component Details	Quantity per 0.5mL	Function
RBD antigen of SARS-CoV-2 (Covid-19)	25 µg	Immunizing Agent
Aluminium Hydroxide gel as Al+++	750 µg	Adjuvant
CpG 1018	750 µg	
Buffer (Tris and NaCl in WFI)	q.s to 0.5 mL	Formulation Buffer

   *Produced in Pichia pastoris (Yeast)
   **RBD antigen of SARS-CoV-2 (Covid-19) is produced using a variant RBD203-N1_XBB.1.5 strain.

5. **Approved Indication of the vaccine:**
   SARS-CoV-2-RBD203-N1_XBB.1.5 vaccine
   CORBEVAX® is indicated for active immunization to prevent Covid-19 disease in individuals of 12 years of age and above to be administered in two dose schedule (0.5mL each) 28 days apart (Day 0 & Day 28).

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6. Posology of vaccine:

Primary Series:

CORBEVAX® vaccination course consists of two separate doses of 0.5 mL. The second dose should be administered at least 4 weeks after the first dose. The vaccine should be administered intramuscularly in the deltoid muscle of upper arm.

7. Instructions for administration:

SARS-CoV-2 (Covid-19) Vaccine [CORBEVAX®] vaccine should be administered intramuscularly in the deltoid muscle of upper arm.

8. Handling of multi dose vials: Not Applicable

9. Concomitant medication (If any):

Concomitant administration of CORBEVAX® with other vaccines has not been studied.

10. Precautions for use:

- Do not administer intravenously, intradermally, or subcutaneously.
- Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization
- The vaccine should remain under medical supervision for at least 30 minutes after vaccination
- Concurrent illness: As with other vaccines, administration of CORBEVAX® should be postponed in individuals suffering from an acute severe febrile illness.
- Thrombocytopenia and coagulation disorders: As with any other intramuscular injection, CORBEVAX® should be given with caution in individuals with thrombocytopenia and coagulation disorders or to individuals on treatment with anticoagulation therapy, because of risk of bleeding or bruising following an intramuscular injection in these individuals.
- Immunocompromised individuals: it is not known if individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to CORBEVAX®. These individuals may have a weaker immune response to the vaccine.

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11. Storage conditions:

Store at +2°C to +8°C. Do Not Freeze. Discard if found frozen. Shake well before use. Do not use the vaccine after the expiry date as mentioned in the label.

12. Shelf life approved:

12 months (single dose - 0.5 ml)

13. Precautions for storage (If any):

Shake well before use and Discard if found frozen. Any unused product or waste material should be disposed as per local regulatory requirements.

14. Brief description on container closure of drug product:

The CORBEVAX® is supplied as liquid and is filled in USP type I glass vials, closed using bromobutyl rubber stoppers and sealed with aluminium flip-off seals. The vaccine is filled into single dose presentation. The single dose presentation is packed into a box of 48 vials.

15. Regulatory Status in India and other Countries:

India:

Restricted Use in Emergency Situation:

CORBEVAX® is indicated for active immunization against Covid-19 disease in individuals aged 5 years and above.

CORBEVAX® is also indicated as a booster dose at ≥6 months after completion of primary immunization with 2 doses of Covishield™ or Covaxin® in individuals aged 18 years and above.

16. The country of origin of imported product, responsible NRA and address (not applicable for indigenous vaccine): Not Applicable

17. Brief summary and conclusion of safety & Immunogenicity/efficacy of Phase I/II, II/III and III clinical trials separately:

SARS-CoV-2 (Covid-19) Vaccine (Variant RBD219-N1-C1).

A. Phase I/II:

- Prospective open label randomised Phase-I seamlessly followed by phase-II study to assess the safety, reactogenicity and immunogenicity when administered intramuscularly in a two-dose schedule (0, 28D) to healthy volunteers (18-55 years age group).

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- The neutralising antibody (nAb) titers were accessed by PSVNT and MNT, and compared with human convalescent sera (HCS) collected from COVID-19 patients. In the PSVNT assay, 275 HCS samples showed a GMT of 126, while in the MNT assay, 37 severe COVID-19 samples showed a GMT of 532. For Corbevax at Day 42, nAb GMTs were 130 (PSVNT) and 537 (MNT), which were comparable to HCS levels.
- The anti-RBD IgG1 vs IgG4 titer data and the significantly higher secretion of cytokine Interferon-gamma vs Interleukin-4 confirm the desired Th1 skew to the overall immune response after two dose primary vaccination series in adults which is also attributed to adjuvants; aluminium hydroxide and CpG1018 after two dose primary vaccination series in adults.
- The immune response demonstrates cross-neutralization potential against Beta strain, a major Variant of Concern. The humoral immune response his highly persistent till at least 12 months post completion of primary vaccination.
- A total of 47 AEs were reported. The majority belonged to SOC general disorders and administration site conditions (35 events; 9.17% of subjects), followed by nervous system disorders (6 events; 1.67%). Musculoskeletal and connective tissue disorders and skin and subcutaneous tissue disorders each accounted for 2 events (0.56%). Most AEs were solicited; two unsolicited events were reported (dyspepsia and COVID-19 infection). Commonly reported PTs were injection site pain, pyrexia and headache. Most AEs occurred between Day 0-56. One serious adverse event (SAE) occurred between Day 56-208. No AEs were reported beyond Day 208 up to Day 393.

SARS-CoV-2 (Covid-19) Vaccine (Variant RBD219-N1-C1).

B. Phase II/III:

- Prospective, multicentre, Phase II (18-55 years) Seamlessly Followed by Phase III (18-80 years) Clinical Study to Evaluate the Immunogenicity and Safety of vaccine When Administered to COVID-19-Negative Adult Subjects.
- The magnitude of humoral immune response post-Corbevax vaccination in the elderly cohort (>45 Yr) is similar to that observed in younger population (18-45 Yr) in terms of increase in anti-RBD IgG concentrations and Neutralizing Antibody Titers post-vaccination
- Significant nAb titers were observed against both Wuhan and Delta and Beta strains.
- The nAb titers against Wuhan strain by PSVNT and MNA method recorded in Phase II & II studies were 285, 329 and 1271 International Units/mL respectively which are indicative of very high vaccine effectiveness in preventing symptomatic infection as shown by the Correlates of Protection evaluation from Moderna and Astra-Zeneca Phase III clinical trials (Moderna study : GMT > 100 IU/mL is

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equivalent to VE of >90%; AZ study : GMT : 61 IU/mL is equivalent to VE of >80%).

- The humoral immune response was skewed towards Th1 category as indicated by the high ratio of anti-RBD IgG1 titers vs. IgG4 titers. Significant cellular immune response was also confirmed in the elderly cohort by both ELISPOT method as well as cytokine expression analysis which showed significant IFN-γ expression by the stimulated PBMC's and minimal expression of IL-4 cytokine and is as expected due to presence of CpG1018 as a co-adjuvant.
- The immune response generated by CORBEVAX vaccination was shown to be highly persistent till 1 Yr post-second dose of vaccination.
- 78 adverse events reported from phase II part of the study, 42 were related to study vaccine and 36 were unrelated. In phase III study, out of 867 total adverse events, 563 events were reported as related to study vaccine and 304 events were reported as unrelated.
- The most commonly reported solicited adverse events in phase II study were Injection site pain, pyrexia and Fatigue. For phase III study were Injection site pain, Headache, Chills, Fatigue, Pyrexia and Myalgia.
- The unsolicited adverse events reported were Pyrexia and Nasopharyngitis in phase II study and Pyrexia, Nasopharyngitis, Headache and Cough in phase III study. No AESIs were reported in phase II and phase III of study.

SARS-CoV-2 (Covid-19) Vaccine (Variant RBD219-N1-C1)

C. Phase III:

- Prospective, Single-blind, Randomized, Active controlled Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Vaccine When Administered to RT-PCR Negative Adult Subjects (18 to 80 years).
- Humoral immune response post-Corbevax vaccination at day-42 is superior to Covishield when assessed for Neutralizing Antibody Titers against the Delta and the Wuhan strain as indicated by the comparison of GMT ratio. Further nAb titers was also measured against the Omicron variant at 3 and 6 months post second-dose of vaccination.
- Vaccine showed comparable seroconversion post vaccination when assessed against anti-RBD IgG response or nAb titers against Wuhan strain and antibody response against the RBD antigen is significantly higher in Corbevax cohort as compared to Covishield.
- Comparison of cellular immune response via Interferon-gamma secreting T cells measured as Spot Forming Units per million PBMC's showed significantly higher response in Corbevax cohort as compared to Covishield cohort in terms of both Median and Average SFU's.

- The persistence data demonstrates significant retention of humoral immune response till 6-months post completion of primary vaccination series in both CORBEVAX and COVISHIELD cohorts.
- A total of 639 subjects were enrolled. In the Corbevax arm, 68/319 subjects (21.3%) reported 100 events, whereas in the Covishield arm, 136/320 subjects (42.5%) reported 192 events.
- A total of 1500 enrolled subjects, 553/1500 (36.9%) subjects reported 1213 events. The most commonly reported adverse events were Injection site pain, Pyrexia, Myalgia, Headache and Fatigue. All the adverse events are mild to moderate in intensity. No AEs and AESI were reported in the study. Most of the solicited adverse events were related to the study vaccine. The safety comparison shown CORBEVAX vaccine is well tolerated and found to be safe.

SARS-CoV-2 (Covid-19) Vaccine (Variant RBD219-N1-C1)

D. Phase III

- A Prospective double-blind randomised Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Single Booster dose of Biological E's CORBEVAX vaccine when Administered to COVID-19- Negative Adult Volunteers Previously vaccinated with 2-doses of either Covishield or Covaxin.
- Significantly superior immune response generated in the CORBEVAX cohort in comparison to the Placebo cohort for both Covishield and Covaxin recipients. The Lower Bound of the 95% confidence interval for the ratio of the GMT's of nAb titers, GMC's of Anti- RBD IgG and corresponding GMFR ratios were >1.0 in CORBEVAX cohort in comparison with the placebo which demonstrates superiority.
- The % of subjects that showed ≥ 2-fold rise in nAb titers as well as Anti-RBD IgG concentrations also was significantly higher in CORBEVAX cohort in comparison to the Placebo cohort.
- nAb titers against the Omicron Variant of Concern, significant increase in nAb titer GMT's as well as % responders were observed after CORBEVAX administration for both Covishield and Covaxin recipient arms in exploratory analysis.
- Cellular immunity assessment conducted by two methods, ELISPOT and Cytokine secretion, post stimulation of the PBMC's present in blood showed significant increase in PBMC's that are responsive to the antigen (SARS-CoV-2 peptides) which demonstrates appropriate Th1 skewed cellular immune response generated post CORBEVAX booster administration in both Covishield and Covaxin recipient arms.
- In COVAXIN-primed subjects (N=208), adverse events were reported in 32/156 subjects (20.5%) receiving CORBEVAX (44 events) and 7/52 subjects (13.5%) receiving placebo (10 events). The most common adverse events in the CORBEVAX group were injection site pain, pyrexia, and headache.

- In COVISHIELD-primed subjects (N=208), adverse events were reported in 28/156 subjects (17.9%) receiving CORBEVAX (38 events) and 8/52 subjects (15.4%) receiving placebo (8 events). The most common adverse events in the CORBEVAX group were injection site pain, headache, myalgia, and fatigue.
- The safety profile of CORBEVAX booster dose, was found to be safe and well tolerated in the subjects who were primed with COVAXIN or COVISHIELD

SARS-CoV-2 (Covid-19) Vaccine (Variant RBD203-N1 XBB.1.5)

E. Phase-III

- A prospective single-blind randomized Phase-III comparative study to evaluate immunogenicity and safety in **5-80 years old individuals.**
- Higher neutralizing antibody titers GMT's at Day-28 and Day-42 time-points (post-first dose and post-second dose of vaccine administration). were observed against the XBB.1.5 strain in subjects vaccinated with XBB.1.5-RBD containing vaccine as it is evident as below:
- Increase in PSVNT GMT and anti-RBD-IgG GMC's from Day-0, Day-28, Day-42 time-point also Increase in % Seroconverted Subjects
- Both XBB.1.5-RBD vaccine and Corbevax-Ancestral strain also demonstrated significant nAb titers in the PSV based assay against the JN.1-strain, in terms of GMT for Day-42 nAb titers.
- The overall magnitude of immune response; measured as PSVNT-GMT and anti-RBD-IgG-GMC; was similar for all three age-groups (Older Adults, Young Adults, Children/Adolescents) for both vaccine cohorts.
- The most commonly reported adverse events in XBB.1.5 RBD subunit vaccine group were Injection site pain [30 AEs in 27 (11.25%) subjects], Pyrexia [13 AEs in 13 (5.42%) subjects], Headache [9 AEs in 9 (3.75%) subject] and Injection site erythema [2 AEs in 2 (0.83%) subjects].
- All the reported adverse events in the study were mild to moderate in their intensity and majority of the adverse events were considered related to the study vaccine by the investigators.

18. Provide brief summary of review process of dossier (CTD format, CMC, CDL, SEC, GMP conclusions etc.):

CDSCO has approved Corbevax-Ancestral Strain vaccines for indication as for active immunization against Covid-19 disease in individuals aged 5 years and above and also indicated as a booster dose at ≥6 months after completion of primary immunization with 2 doses of Covishield or Covaxin in individuals aged 18 years and above for restricted use in emergency situation.

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Corbevax XBB.1.5 (SARS-CoV-2 RBD203-N1_XBB.1.5) is also approved for indication as for active immunization to prevent COVID–19 disease in individuals of 5 years of age and above who have received primary vaccination series & to be administered in two dose schedule (0.5mL each) 28 days apart (Day 0 & Day 28) for restricted use in emergency situation as per clause 2 (A), 2 (B) of second schedule of NDCT Rules 2019.

In view of above considering provisions of Second Schedule, clause 3(B)(I)(A), (B), (C) of NDCT Rules, 2019 and based on the review of the CMC data which includes manufacturing, testing, process validation & stability data of drug substance and drug product, pre-clinical toxicology, clinical trial studies which includes data on Anti-RBD IgG, neutralizing Antibody titers, seroconversion, cross neutralization data on(Prototype-Wuhan Strain, Omicron strains, XBB.1.5 & JN.1 strains), post marketing safety data and test report from CDL, Kasauli for single dose presentation of XBB 1.5 strain vaccine, the recommendations of SEC(COVID) dated 06.05.2025 and considering the recommendations of NTAGI on the usage of the covid-19 vaccine in private sector & the programmatic use of Corbevax vaccine (ancestral) in the vaccination program for the age group of 12 to 14 years, the overall benefit-risk ratio of the vaccine was considered favourable for granting New Drug permission as per NDCT Rules, 2019.