


Summary of Product Characteristics (SmPC)	 <i>Biological E. Limited</i>
SARS-CoV-2 (Covid-19) Vaccine [CORBEVAX™]	

1. NAME OF THE MEDICINAL PRODUCT

SARS-CoV-2 (Covid-19) Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 mL Contains

RBD antigen of SARS-CoV-2 (Covid-19) ¹	25 µg
Aluminium Hydroxide gel as Al ⁺⁺⁺	750 µg
CpG 1018	750 µg
Buffer (Tris and NaCl in WFI)	q.s to 0.5 mL

¹ Produced in *Pichia pastoris* (Yeast)

3. PHARMACEUTICAL FORM

SARS-CoV-2 (Covid-19) Vaccine is a whitish or almost white translucent liquid in which the mineral carrier tends to settle down slowly and should be free from particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications


CORBEVAX™ is indicated for active immunization against Covid-19 disease in Adolescents and Adults aged ≥ 12 years and above for restricted use in emergency situation.

4.2 Posology and Method of Administration

Posology: 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.

4.3 Contraindications

- Hypersensitivity to any constituents of the vaccine
- Pregnant and lactating women
- During fever or severe infection
- Individuals below 12 years
- Have received another Covid-19 vaccine
- Are immunocompromised or are on a medicine that affects your immune system
- Have a bleeding disorder or are on a blood thinner

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4.4 Special Warning and 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 vaccinee should remain under medical supervision for at least 30 minutes after vaccination

CORBEVAX™ should be shaken well to obtain a uniform, whitish translucent suspension before use. Prior to administration, the vaccine vial should be visually checked for complete suspension and presence of any particulate matter or other coloration, if any. If in doubt, do not use the contents of the vial. Sterile needle and syringe should be used for withdrawal of the vaccine.

4.5 Interaction with other Medicinal Products/ other Forms of Interaction

No interaction studies have been performed. Concomitant administration of CORBEVAX™ with other vaccines has not been studied.

4.6 Use in Special Populations (such as pregnant women, lactating women)

Safety and effectiveness have not been established in pregnant women, nursing mothers. It is not known whether the vaccine is excreted in human milk.


4.7 Effect on Ability to Drive and Use Machines

No studies on the effect of CORBEVAX™ on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Clinical Trial Experience: The safety of CORBEVAX™ was established in a controlled clinical trials in adults aged 12 years to 80 years. Within each system organ class (SOC) the adverse reactions were ranked under headings using the following convention:

Very common	≥ 10%
Common	≥ 1% and < 10%
Uncommon	≥ 0.1% and < 1%
Rare	≥ 0.01% and < 0.1%

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Systemic:

Common (may affect up to 1 in 10 people)

- Fever/Pyrexia
- Headache
- Fatigue
- Body pain
- Myalgia
- Nausea

Uncommon (may affect up to 1 in 100 people)

- Arthralgia
- Urticaria
- Chills
- Lethargy

Local:

Very common (may affect up to ≥ 1 in 10 people)

- Injection site pain

Common (may affect up to 1 in 10 people)

- Injection site erythema

Uncommon (may affect up to 1 in 100 people)


- Injection site swelling
- Injection site rash
- Injection site pruritus

Rare (may affect up to 1 in 1000 people)

- Injection site irritation

Summary of safety profile:

In a phase I / II clinical study (BECT062) conducted in 360 subjects aged ≥ 18 to ≤ 65 years to assess the safety, reactogenicity and immunogenicity and to select the optimum formulation of BE's SARS-CoV-2 (Covid-19), all the four formulations were found to be safe and well tolerated.

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In a phase II/III Clinical study (BECT069) conducted in 1268 subjects aged 18-80 years, a total of 51 adverse events were reported in 27 (27%) study subjects (phase II) and 532 adverse events were reported in 255 (21.8%) study subjects (phase III). In which 34 solicited adverse events were reported in 20 (20%) subjects and 455 solicited adverse events reported in 229 (19.6%) subjects in Phase II and phase III parts of the study respectively. Majority of adverse events are mild to moderate in intensity and no severe AEs were reported in the study. No SAEs and AESI were reported in the study (See Table 1).

Table 1: Adverse drug reactions from Phase II & III study

MedDRA SOC	Frequency	Adverse reactions
General disorders and administration site conditions	Very common	Injection site pain
	Common	Fatigue, Pyrexia ^b , Chills
	Uncommon	Injection site swelling, Pain, Injection site erythema
Nervous system disorders	Common	Headache
	Rare	Lethargy
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia
	Uncommon	Pain in extremity ^a
	Rare	Back pain ^a
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough ^a , Dyspnoea ^a , Oropharyngeal pain (Sore throat) ^a
Infections and infestations	Uncommon	Nasopharyngitis (Common cold) ^a
	Rare	Pharyngitis (Throat infection) ^a
Gastrointestinal disorders	Uncommon	Nausea, Diarrhoea
Metabolism and nutrition disorders	Rare	Decreased appetite ^a
Skin and subcutaneous tissue disorders	Rare	Urticaria ^a

^a : Unsolicited event

^b : Pyrexia includes feverishness (very common) and fever $\geq 100.4^{\circ}\text{F}$ (common)

All the unsolicited events were unrelated to the Vaccine.

In a phase III active comparator study (BECT074) conducted in 2140 subjects aged 18 to 80 years, the safety of CORBEVAX™ was found comparable to the comparator vaccine (Covishield™). All the adverse events were mild to moderate in intensity and no severe AEs were reported in the study. No AESI were reported in the study. Most of the solicited adverse events were related to the study vaccine (See Table 2).


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Table 2: Adverse drug Reactions from Phase III Superiority Study

MedDRA SOC	Frequency	Adverse reactions
General disorders and administration site conditions	Very common	Injection site pain, Pyrexia ^b
	Common	Injection site erythema, Injection site pruritus, Headache, Injection site swelling, Fatigue
	Uncommon	Injection site warmth, Chills, Injection site rash, Pain
	Rare	Irritability, Injection site irritation
Nervous system disorders	Common	Headache
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Common	Arthralgia
	Rare	Back pain ^a
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough ^a , Oropharyngeal pain (Sore throat) ^a
	Rare	Rhinorrhoea (running nose), Throat irritation ^a , Sneezes ^a
Infections and infestations	Uncommon	Nasopharyngitis (Common cold) ^a
Gastrointestinal disorders	Common	Nausea,
	Uncommon	Upper abdominal pain ^a , Diarrhoea ^a , Vomiting ^a ,
Skin and subcutaneous tissue disorders	Uncommon	Urticaria
	Rare	Acne ^a , Rash

^a : Unsolicited event


^b : Pyrexia includes feverishness (very common) and fever $\geq 100.4^{\circ}\text{F}$ (common)

In a phase II/III study (BECT072) conducted in 624 subjects aged ≥ 5 to < 18 years in two age cohorts (≥ 5 to < 12 and ≥ 12 to < 18 years) to prove safety, tolerability and reactogenicity of the vaccine against placebo, the interim results from 200 subjects (150 in vaccine arm and 50 in placebo arm) indicated that, there was no difference in the safety profile when compared to the data of earlier clinical trials conducted in adults.

All the unsolicited events were unrelated to the vaccine.

4.9 Overdose

No case of overdose has been reported. There is no specific treatment for an overdose with CORBEVAX™. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action


The receptor-binding domain (RBD) in the S1 subunit of the SARS-CoV-2 spike (S) protein binds to the ACE-2 receptor on human cells which initiates the virus infection and is the most important target for developing a SARS vaccine. In particular, RBD of S protein contains the critical neutralizing domain (CND), which is able to induce highly potent neutralizing antibody response and cross-protection against divergent SARS-CoV-2 strains. RBD-based subunit vaccine is expected to be safer than other vaccines that may induce Th2-type immunopathology. CORBEVAX™ targets the S1 subunit of the SARS-CoV-2 spike (S) protein leading to induction of protective immunity against severe Covid-19 infection.

5.2 Pharmacodynamic Properties

Covid-19 disease is caused due to SARS-CoV-2 virus infection. CORBEVAX™ is based on classical vaccine technology of a protein antigen, SARS-CoV-2 Spike RBD, adsorbed to the adjuvants, has been studied in Phase I/II, II/III and III clinical studies for safety, reactogenicity and immunogenicity and found to be safe and immunogenic.

In a Phase I/II clinical study (BECT062) is conducted in 360 subjects aged ≥ 18 to ≤ 65 years to assess the safety, reactogenicity and immunogenicity and to select the optimum formulation of BE's SARS-CoV-2 (Covid-19) Vaccine. The immunogenicity testing indicated the optimum formulation elicited a significant humoral and cellular immune response.

In a Phase II/III Clinical study (BECT069) conducted in 1268 subjects aged 18-80 years, the immunogenicity was evaluated in 100 subjects in Phase II part in 18-55 year cohort and in a subset of population (elderly cohort aged >45 Year) in Phase III trial. Similar overall immune response was observed in both younger population (18-45 Year) and elderly population (45-80 Year) 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 which has also been consistently noted in Phase I/II studies of CORBEVAX™. The interim Wuhan-nAb GMT was indicative $> 90\%$ vaccine effectiveness in preventing symptomatic infection as shown by the Correlates of Protection evaluation from Covid-19 vaccine efficacy trial analysis. In the Phase III part of the study, pre-vaccination Anti-RBD IgG and nAb titers were higher than the Phase II study. However, significant increase in IgG and

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nAb titers were still observed post vaccination which indicates excellent immune response generated by CORBEVAX™ (See Table 3). The sub-set of subjects assessed for immunogenicity also elicited a significant humoral and cellular immune response.

Table 3: Summary of Immunogenicity from Phase II/III Study

a) Summary of Anti-RBD IgG concentration

Time point	Statistic	CORBEVAX™	% SCR
Phase II part			
Base Line (Day 0)	N	98	NA
	GMC (EU/mL)	945	
	95% CI	788-1134	
Day-42	N	98	95%
	GMC (EU/mL)	26448	
	95% CI	19858-35223	
Phase III part			
Base Line (Day 0)	N	65	NA
	GMC (EU/mL)	4287	
	95% CI	3137-5857	
Day-42	N	65	89 %
	GMC (EU/mL)	61138	
	95% CI	47485-78715	

N: Number of subjects

GMC: Geometric Mean Concentration

CI: Confidence Interval

SCR: Seroconversion Rate

NA: Not Applicable

b) Summary of Neutralizing Antibody (nAb) Titers against Wuhan

Time point	Statistic	CORBEVAX™
Phase II part		
Base Line (Day-0)	N	98
	GMT	67
	95% CI	52-88
Day-42	N	98
	GMT	1338
	95% CI	917-1954
Phase III part		
Base Line (Day-0)	N	65
	GMT	470
	95% CI	330-670
Day-42	N	65
	GMT	5166
	95% CI	3830-6967
	% SCR	86 %


N: Number of subjects

GMT: Geometric Mean Titre

CI: Confidence Interval

SCR: Seroconversion Rate

NA: Not Applicable

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The sub-set of 20 subjects from Phase II part were tested for Neutralizing Antibody (nAb) Titers against Wuhan, Delta and Beta variants. The GMT was found to be 2351, 1487 and 511 respectively against Wuhan, Delta and Beta variants in this sub-set. The Sub-set of 65 subjects aged in elderly cohort (> 45 years age) from Phase III part were also tested for Neutralizing Antibody (nAb) Titers against Delta variant, in which the GMT was found to be 2341 (1614-3395).

In a Phase III superiority study (BECT074) conducted in 2140 subjects aged 18 to 80 years to prove the immunogenic superiority and safety, CORBEVAX™ demonstrated superior immune response in comparison to Covishield™ when assessed for Neutralizing Antibody Titers against the Wuhan and Delta variants in terms of GMT's (See Table 4). The sub-set of subjects assessed for immunogenicity also elicited a significant humoral and cellular immune response. CORBEVAX™ nAb GMT against Wuhan strain was indicative of vaccine effectiveness of >90% for prevention of symptomatic infections based on the Correlates of Protection assessment performed as part of Covid-19 vaccine efficacy trial analysis.

Table 4: Summary of Phase III Immunogenic Superiority Study

a) Summary of Anti-RBD IgG concentration


Time point	Statistic	CORBEVAX™	COVISHIELD™
Base Line (Day-0)	N	304	307
	GMC (EU/mL)	1439	1503
	95% CI	1268-1633	1316-1716
Day-42	N	304	307
	GMC (EU/mL)	24478	16203
	95 % CI	21075-28431	14428-18196
	% SCR	91%	88%

N: Number of subjects GMC: Geometric Mean Concentration
CI: Confidence Interval SCR: Seroconversion Rate NA: Not Applicable

b) Summary of Neutralizing Antibody (nAb) Titers

Time point	Statistic	CORBEVAX™		COVISHIELD™	
		Wuhan	Delta	Wuhan	Delta
Base Line (Day-0)	N	303		307	
	GMT	85	ND	75	ND
	95% CI	75-96		65-86	
Day-42	N	301	301	304	304
	GMT	2123	874	1833	562
	95% CI	1801-2514	724-1055	1632-2089	482-657
	% SCR	95%	NA	94%	NA

N: Number of subjects GMT: Geometric Mean Titre ND: Not Done

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CI: Confidence Interval SCR: Seroconversion Rate NA: Not Applicable

CORBEVAX™ showed comparable seroconversion and higher anti-RBD IgG concentration in comparison to Covishield™ post vaccination.

In a Phase II/III clinical study (BECT072) conducted in 624 subjects aged ≥ 5 to < 18 years in two age cohorts (≥ 5 to < 12 and ≥ 12 to < 18 years) to prove the safety, tolerability and immunogenicity, the interim results indicated that significant increase in IgG and nAb titers (Wuhan and Delta variants) were observed post vaccination (at Day-42) which indicates excellent immune response generated by CORBEVAX™ in this age group and is inline with IgG and nAb titers observed in earlier clinical trials observed in Adults (See Table 5).

Table 5: Summary of Interim study results of Phase II/III study in ≥ 12 to < 18 years

a) Summary of Anti-RBD IgG concentration

Time point	Statistic	CORBEVAX™
≥ 12 to < 18 years		
Base Line (Day-0)	N	191
	GMC (EU/mL)	939
Day-42	N	191
	GMC (EU/mL)	18991
	% SCR	93%

N: Number of subjects GMC: Geometric Mean Concentration SCR: Seroconversion Rate

b) Summary of Neutralizing Antibody (nAb) Titers


Time point	Statistic	CORBEVAX™	
		Wuhan	Delta
≥ 12 to < 18 years			
Base Line (Day-0)	N	169	NA
	GMT	50	NA
Day-42	N	169	169
	GMT	1034	420

N: Number of subjects GMT: Geometric Mean Titre NA: Not Applicable

CORBEVAX™ nAb titers in terms of GMT were indicative of vaccine effectiveness of $> 90\%$ based on the Correlates of Protection assessment performed as part of Covid-19 vaccine efficacy trial analysis.

5.3 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

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5.4 Preclinical Safety Data

Single dose toxicity studies in Rats and repeat dose toxicity studies in Rats and Rabbits were conducted. Based on the toxicity studies conducted, it is concluded that the vaccine formulation did not produce any adverse effects at dose level of 0.5 mL.

Immunogenicity studies are also conducted with the vaccine in Rats and Mice. Based on the immunogenicity studies, the vaccine shown higher antibody titre (IgG and NT₅₀) when compared to Pre immune sera group and Placebo's groups. CORBEVAX™ efficacy in prevention of SARS-CoV-2 infection was also demonstrated in virus challenge studies conducted in Non-Human Primates which showed absence or significant reduction of viral RNA in lung tissue or nasal/throat swabs in vaccinated animals in comparison to unvaccinated controls.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

The vaccine contains RBD antigen of SARS-CoV-2 (Covid-19) and is produced in *Pichia pastoris* (Yeast).

List of excipients:


- Aluminium Hydroxide gel as Al⁺⁺⁺
- CpG 1018
- Buffer (Tris and NaCl in WFI)

6.2 Incompatibilities

The product should not be mixed with any other medicinal products or active immunizing agents.

6.3 Shelf Life

Shelf life of CORBEVAX™ is 12 months from the date of manufacturing. The manufacturing date of the vaccine is indicated on the label and carton of the product.

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6.4 Special Precautions for Storage

Store at +2°C to +8°C. DO NOT FREEZE. Discard if found frozen. Shake well before use. Keep out of reach of children. Multi dose vials should be used within 6 hours once opened. Do not use the vaccine after the expiry date as mentioned in the label.

6.5 Nature and Contents of Container

The CORBEVAX™ is supplied as liquid and is filled in USP type I glass vials, closed using bromobutyl rubber stoppers and sealed with aluminum flip-off seals. The vaccine is offered in the following presentations:

- Single dose vial (0.5 mL)
- Ten dose vial (5 mL)
- Twenty dose vial (10 mL)

6.6 Special Precautions for Disposal

Any unused product or waste material should be disposed as per local regulatory requirements

7. MARKETING AUTHORISATION HOLDER

Biological E. Limited

Regd. office:

18/1 & 3, Azamabad, Hyderabad,
Telangana - 500 020, INDIA.

Manufacturing Site Address:

BE's Shameerpet site. Plot No. 1, Biotech Park, Phase II, Kolthur Village - 500 078, Shameerpet, Medchal-Malkajgiri District, Telangana, INDIA. Web site: www.biologicale.com	BE's Azamabad site: M/s. Biological E. Limited 18/1&3, Azamabad, Hyderabad, Telangana -500020 Tel: 91-40-3021 3999; Fax: 91-40-2761 5309
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8. MARKETING AUTHORISATION NUMBER(S)

MF/BIO/21/000136

9. DATE OF FIRST AUTHORISATION

Date of Approval for adults aged \geq 18 years and above : 28-Dec-2021

Date of Approval for adolescents aged \geq 12 years to < 18 years : 21-Feb-2022