For the Use Only by of a Registered Medical Practitioner or a Hospital or a Laboratory

RESTRICTED USE IN EMERGENCY SITUATION OF COVID-19

Lyophilized mRNA Vaccine for Injection (COVID-19) 10 µg/Dose [10 µg/0.1 mL] [Omicron variant - sublineage BA.1]

GEMCOVAC®-OM

AS A BOOSTER FOR THE PREVENTION OF COVID-19 DISEASE IN INDIVIDUALS 18 YEARS OF AGE AND OLDER WHO HAVE RECEIVED EITHER COVAXIN® OR COVISHIELD™ AS PRIMARY VACCINATION

1. GENERIC NAME

Lyophilized mRNA Vaccine for Injection (COVID-19) 10 µg/ Dose [10 µg/ 0.1 mL] [Omicron variant - sublineage BA.1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.1 ml contains:

mRNA (Omicron variant sublineage BA.1)	10.0 µg
Excipients	q.s.

The *in vitro* transcribed mRNA encodes for the viral Spike (S) glycoprotein of the omicron variant (BA.1) of SARS-CoV-2.

3. DOSAGE FORM AND STRENGTH

GEMCOVAC®-OM is a lyophilized powder that needs to be reconstituted with 0.7 mL of Sterile Water for Injections I.P. before administration. The reconstituted solution is off white liquid free from any visible particles. Each dose of 0.1 mL contains 10 µg of GEMCOVAC®-OM mRNA vaccine (Omicron variant).

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

GEMCOVAC®-OM is indicated as a booster for active immunization for the prevention of COVID-19 in individuals 18 years of age and older who have received either COVAXIN® or COVISHIELD™ as primary vaccination.

4.2 Posology and method of administration

Posology

GEMCOVAC®-OM is indicated as a single booster dose in individuals aged ≥ 18 years administered at least 4 months after completion of primary vaccination with either COVISHIELD™ or COVAXIN®.

Method of administration

GEMCOVAC®-OM should be administered (0.1 mL) by intradermal route only using Needle- free Injection device Tropis® (PharmaJet, USA).

4.3 Contraindications

- Hypersensitivity to any constituents of GEMCOVAC®-OM.
- Individuals below 18 years of age.

4.4 Special warnings and precautions for use

- GEMCOVAC®-OM should not be administered intravenously, intramuscularly or subcutaneously.
- Hypersensitivity and Anaphylaxis: There is a risk of hypersensitivity reactions due to the constituents of GEMCOVAC®-OM. Supervision and if needed the appropriate medical treatment should be provided to all the vaccine recipients after immunization.
- Concurrent Illness: As with other vaccines, administration of GEMCOVAC®-OM should be postponed in individuals suffering from an acute severe febrile illness.
- GEMCOVAC®-OM should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy.
- Immunocompromised Individuals: It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.
- Anxiety related reactions: Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the vaccination. It is important that precautions are in place to avoid injury from fainting.
- Interchangeability: There are no safety, immunogenicity or efficacy data to support interchangeability of GEMCOVAC®-OM with other COVID-19 vaccines.
- Reconstitution:
  5 Dose: GEMCOVAC®-OM is available as a lyophilized powder which needs to be reconstituted with Sterile Water for Injection I.P. Withdraw 0.7 mL of sterile water for Injection and reconstitute the vial. Gently swirl the vial intermittently for approximately 180 seconds till all the lyophilized contents are dissolved and no particles are visible. The solution should be off white liquid free from any visible particles. Administer 0.1mL of the reconstituted vaccine solution intradermally within 6 hours of reconstitution to the recipient. If not administered immediately after reconstitution, keep reconstituted vaccine back at +2ºC to +8ºC. This vaccine is multi-dose. It will be used for dosing up to 5 recipients who must be dosed on same day within 6 hours of reconstitution.

4.5 Drug interactions

The safety, immunogenicity and efficacy of co-administration of GEMCOVAC®-OM with other vaccines or medications has not been evaluated.

4.6 Use in special populations

Safety, efficacy and immunogenicity has not been established in pregnant women and nursing mothers. It is unknown if GEMCOVAC®-OM is excreted in human milk.

Paediatric population: The safety and immunogenicity of GEMCOVAC®-OM has not been established in children and adolescents < 18 years of age.

Elderly population: No dose adjustment is required for the elderly.

4.7 Effects on ability to drive and use machines

No studies on the effect of GEMCOVAC®-OM on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Safety data from Phase II Clinical Trial

The Phase II clinical trial was conducted in 140 participants. The safety and immunogenicity of GEMCOVAC®-OM was compared with the GEMCOVAC®-19 which has received Emergency Use Authorization from Indian Regulatory Authority. The participants were randomized to the two vaccine arms in a 1:1 ratio. Participants included in this study received either COVAXIN® or COVISHIELD™ as their primary vaccination (two doses) at least 4 months back.

Table 1. Phase II clinical trial demography

Demography	GEMCOVAC®-OM (n = 70)	GEMCOVAC®-19 (n = 70)
Age [Median (min., max.)]	32 (20, 49)	30 (20, 45)
Male, %	87.1%	91.4%
Weight [Mean (SD)]	64.8 (5.07)	63.7 (5.17)
BMI [Mean (SD)]	23.2 (1.67)	23.0 (1.54)

The clinical trial is ongoing and safety data up to Day 90 has been analyzed.

Local Solicited Adverse Events: A total of 3 participants (4.3%) receiving GEMCOVAC®-OM experienced at least one solicited local adverse event (AE) compared to 5 participants (7.1%) in the GEMCOVAC®-19 arm.

COVAXIN® primed subjects (n = 28): Only 1 local solicited AE (7.1%) was reported in a subject who received GEMCOVAC®-19 as a booster dose. It was mild in intensity.

COVISHIELD™ primed subjects (n = 112): 7 participants [GEMCOVAC®-19: 4 (7.1%); GEMCOVAC®-OM: 3 (5.4%)] reported at least one local solicited AE. Out of these 7 AEs, 4 were of Grade 1 intensity (mild) in GEMCOVAC®-19 and 2 AEs of Grade 1 intensity in GEMCOVAC®-OM. Only 1 AE of Grade 2 intensity (moderate) was observed in GEMCOVAC®-OM arm.

Pain at the injection site was the most common local solicited adverse event noted in 3 (4.3%) and 5 (7.1%) subjects in GEMCOVAC®-OM and GEMCOVAC®-19 groups respectively. No Grade 3 or higher adverse event was observed in participants receiving GEMCOVAC®-OM.

Systemic Solicited Adverse Events: A total of 6 participants [GEMCOVAC®-19: 4 (5.7%); GEMCOVAC®-OM: 2 (2.9%)] reported at least one systemic solicited AE.

COVAXIN® primed subjects (n = 28): No systemic solicited adverse events were reported.

COVISHIELD™ primed subjects (n = 112): 2 participants (2.9%) receiving GEMCOVAC®-OM experienced at least one solicited systemic adverse event compared to 4 participants (5.7%) in the GEMCOVAC®-19 arm. One AE in 1 (1.8%) subject who received GEMCOVAC®-OM as a booster dose was moderate in nature and rest of the AEs were mild.

In the participants who received GEMCOVAC®-19, fatigue was observed in 1 (1.4%) and pyrexia was observed in 1 (1.4%) subject. In both GEMCOVAC®-OM and GEMCOVAC®-19 arms, myalgia and headache were observed in 1 (1.4%) subject each. No Grade 3 or higher adverse event was observed in participants receiving GEMCOVAC®-OM.

No Serious Adverse Events (SAEs) or Adverse Event of Special Interest (AESI) or COVID-19 events were reported up to 3 months after the booster dose in either GEMCOVAC®-OM or GEMCOVAC®-19 arm.

Safety data from Phase III Clinical Trial

The Phase III clinical trial was conducted in 3140 participants who were randomized to receive either GEMCOVAC®-OM or COVISHIELD™. In Arm I, GEMCOVAC®-OM was administered as a booster dose to participants whose primary vaccination was either COVAXIN® or COVISHIELD™. In Arm II, COVISHIELD™ was administered as a booster to participants whose primary vaccination was COVISHIELD™.

Table 2. Phase III clinical trial demography

Demography	GEMCOVAC®-OM (n = 2990)	COVISHIELD™ (n = 133)
Age, Median (min., max.)	32.0 (18.0, 81.0)	32.0 (19.0, 57.0)
Male, %	68.2%	79.7%
Weight, Mean (SD)	62.6 (10.10)	63.9 (10.63)
BMI, Mean (SD)	23.6 (3.43)	23.8 (3.52)
Co-morbid Conditions		
Anemia, n (%)	1 (0.03%)	0 (0%)
Hypothyroidism, n (%)	1 (0.03%)	1 (0.75%)
Diabetes Mellitus, n (%)	1 (0.03%)	0 (0%)
Obesity, n (%)	1 (0.03%)	0 (0%)
Hypertension, n (%)	7 (0.23%)	0 (0%)

The clinical trial is ongoing and safety data up to Day 90 has been analyzed.

Local Solicited Adverse Events: A total of 353 (11.8%) participants receiving GEMCOVAC®-OM and 18 (13.5%) participants receiving COVISHIELD™ experienced at least one local solicited adverse event.

COVAXIN® primed subjects (n = 622): A total of 73 (11.7%) participants who received GEMCOVAC®-OM as booster dose experienced at least one local solicited AE. All of them were of mild and moderate in intensity.

COVISHIELD™ primed subjects (n = 2501): A total of 280 (11.8%) participants who received GEMCOVAC®-OM and 18 (13.5%) participants who received COVISHIELD™ experienced at least one local solicited AE. Most of the local AEs were either mild or moderate in intensity.

In the participants receiving GEMCOVAC®-OM, pain at the injection site was the most common local solicited reaction in 275 (9.2%), followed by redness in 86 (2.9%), pruritus in 61 (2.0%), swelling in 48 (1.6%), warmth in 3 (0.1%) and bruising in 1 (0.1%) participant. Most of the local solicited adverse events were of Grade 1 and 2 severities. Only one case of Grade 3 (injection site bruising) event was observed in participant receiving GEMCOVAC®- OM.

Systemic Solicited Adverse Events: A total of 353 (11.8%) participants receiving GEMCOVAC®-OM and 16 (12.0%) participants receiving COVISHIELD™ observed at least 1 systemic solicited adverse event.

COVAXIN® primed subjects (n = 622): A total of 69 (11.1%) participants who received GEMCOVAC®-OM as booster dose experienced at least one systemic solicited AE. All of them were of mild and moderate in intensity.

COVISHIELD™ primed subjects (n = 2501): A total of 300 (12%) participants [GEMCOVAC®-OM: 284 (12.0%); COVISHIELD™: 16 (12.0%)] experienced at least one systemic solicited AE. All of them are mild and moderate in intensity.

In participants receiving GEMCOVAC®-OM, the most common systemic solicited event was fever in 197 (6.6%) followed by headache in 133 (4.4%), myalgia in 64 (2.1%), fatigue in 49 (1.6%), chills in 20 (0.7%), arthralgia in 21 (0.7%), nausea in 5 (0.2%), malaise in 3 (0.1%), vomiting in 2 (0.1%) and influenza like illness in 2 (0.1%). All of the systemic solicited AEs were of Grade 1 and 2 severities. No Grade 3 or higher adverse events were observed in participants receiving GEMCOVAC®-OM.

Unsolicited Adverse Events: A total of 28 (0.94%) participants receiving GEMCOVAC®-OM and 2 (1.5%) of participants receiving COVISHIELD™ observed at least one unsolicited adverse event.

COVAXIN® primed subjects (n = 622): 4 AEs of systemic unsolicited Adverse Events were reported in 4 (0.64%) subjects who received GEMCOVAC®-OM as booster dose. Three unsolicited AEs were of mild category and 1 unsolicited AE was of moderate category.

COVISHIELD™ primed subjects (n = 2501): 26 systemic unsolicited AEs [GEMCOVAC®-OM: 24 (1.01%); COVISHIELD™: 2 (1.5 %)] were reported. Most of them were mild and moderate in nature except 2 severe in GEMCOVAC®-OM arm.

Serious Adverse Events (SAE): Three SAEs was reported in GEMCOVAC®-OM Arm (Omphalitis with umbolith, spontaneous abortion and pulmonary koch) which were not related to study vaccine.

Adverse drug reactions observed during the clinical trials were ranked using the following conventions:

Very Common : ≥1/10
Common : ≥1/100 to < 1/10
Uncommon : ≥1/1000 to < 1/100
Rare : ≥1/10000 to < 1/1000

Table 3. Adverse Events Observed in Phase III trial with GEMCOVAC®-OM

MedDRA System Organ Class	Frequency	Adverse Event
General Disorders and Administration Site Conditions	Common	Pain/Tenderness, Redness/Erythema, Swelling/Induration, Fatigue, Pruritus, Pyrexia
	Uncommon	Warmth, Chills, Malaise
Musculoskeletal and connective tissue disorders	Common	Myalgia
	Uncommon	Arthralgia
Nervous System Disorders	Common	Headache
Gastrointestinal Disorders	Uncommon	Vomiting, Nausea
Skin And Subcutaneous Tissue Disorders	Uncommon	Rash

No cases of myocarditis/pericarditis (Adverse Event of Special Interest) or COVID-19 cases were reported in the Phase III clinical trial.

4.9 Overdose

There is no data on overdose of GEMCOVAC®-OM.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

GEMCOVAC®-OM uses the monovalent Omicron variant (BA.1) of the viral S - protein of the SARS-CoV-2 virus as antigen, which is reported to interact with host cells receptors (ACE-2). It uses a self-amplifying mRNA platform for slow and sustained release of S-protein for longer duration along with CLNE system for targeted vaccine delivery. Once administered intradermally, the in vitro transcribed mRNA encoding the S-protein (omicron variant) is translated in the cytosol of the cells utilizing the cellular translational machinery. The S-protein synthesized represents the antigen, which then elicits the potent humoral and cellular immune responses.

5.2 Pharmacodynamic properties

Immunogenicity of Phase II Clinical Trial

In the Phase II study, the safety and immunogenicity of GEMCOVAC®-OM was compared to GEMCOVAC®-19. A total of 140 participants who were ≥ 18 years and received COVAXIN® or COVISHIELD™ as their primary vaccination were randomized in a 1:1 ratio.

Anti-Spike IgG Antibodies: In the overall population, at Day 29, a statistically significant increase was seen in participants receiving both GEMCOVAC®-OM and GEMCOVAC®-19. The increase was greater with GEMCOVAC®-OM compared to GEMCOVAC®-19. The Least Square Geometric Mean Ratio (LSGMR; GEMCOVAC®-OM/GEMCOVAC®-19) was 3.40 (95% CI: 2.79; 4.13) and was statistically significant ($p < 0.0001$) using ANCOVA with baseline titers as covariates.

Similar findings were observed on performing subgroup analysis in participants who received COVAXIN® and COVISHIELD™ as their primary immunization (Table 4).

Table 4. Anti-Spike IgG Antibodies in the Phase II study

Time point	Primary vaccination COVAXIN		Primary vaccination COVISHIELD		Overall	
	GEMCOVAC-OM (n=14)	GEMCOVAC-19 (n=14)	GEMCOVAC-OM (n=56)	GEMCOVAC-19 (n=56)	GEMCOVAC-OM (n=70)	GEMCOVAC-19 (n=70)
Baseline, GMT (95% CI)	23227.30 (13801.11, 39091.62)	30137.08 (19780.52, 45916.06)	32046.95 (24722.41, 41541.55)	37213.34 (29787.09, 46491.04)	30048.94 (23910.65, 37763.03)	35676.25 (29401.69, 43289.84)
Day 29, GMT (95% CI)	229202.48 (197702.41, 265721.49)	59528.52 (36959.75, 95878.49)	248405.33 (230771.99, 267386.04)	80365.02 (63797.84, 101234.40)	244440.18 (229122.30, 260782.13)	75683.05 (61687.58, 92853.78)

Seroconversion: Seroconversion rates were assessed by ≥2- fold rise in antibody (Anti-Spike IgG) titers at Day 29 from baseline. More subjects (65 [92.9%]) in the GEMCOVAC®-OM group achieved ≥ 2-fold rise in antibody titers as compared to subjects (40 [57.1%]) in the GEMCOVAC®-19 group. At Day 29, GMFR (Post-booster/Pre-booster vaccination) was greater in GEMCOVAC®-OM (8.13) compared to GEMCOVAC®-19 (2.12). The seroresponse rate difference between GEMCOVAC®-OM and GEMCOVAC®-19 calculated using Miettinen-Nurminen method was 35.71 (95% CI: 22.35; 48.52) which was statistically significant ($p < 0.0001$).

cPASS™ Neutralization Assay (Omicron Variant BA.1): The cPASS™ SARS-CoV-2 Surrogate Neutralization Antibody assay (Genscript) measures the neutralizing antibodies in blood sera of the participants. Rise in neutralizing antibodies (mean %) against SARS-CoV-2 from baseline to Day 29 was higher in GEMCOVAC®-OM (73.4% to 93.9%) as compared to GEMCOVAC®-19 (76.9% to 84.0%). The difference of mean % change from baseline between GEMCOVAC®-OM and GEMCOVAC®-19 was 10.9 (95% CI: 7.02, 14.87) and was statistically significant ($p < 0.0001$).

Similar rise in neutralizing antibodies were observed on performing subgroup analysis on participants receiving COVAXIN® and COVISHIELD™ as their primary vaccination (Table 5).

Table 5. Neutralization by cPASS™ assay in Phase II study

Time point	Primary vaccination COVAXIN®		Primary vaccination COVISHIELD™		Overall	
	GEMCOVAC-OM (n=14)	GEMCOVAC-19 (n=14)	GEMCOVAC-OM (n=56)	GEMCOVAC-19 (n=56)	GEMCOVAC-OM (n=70)	GEMCOVAC-19 (n=70)
Baseline, Mean % (95% CI)	74.9 (61.78, 87.99)	82.5 (74.51, 90.40)	73.0 (65.90, 80.09)	75.5 (68.81, 82.18)	73.4 (67.26, 79.48)	76.9 (71.34, 82.43)
Day 29, Mean % (95% CI)	93.9 (91.66, 96.07)	88.2 (81.24, 95.16)	93.9 (92.41, 95.47)	82.9 (77.66, 88.17)	93.9 (92.65, 95.20)	84.0 (79.58, 88.36)

Cellular Immune Responses: T-cell responses against the spike protein were assessed by using flow-cytometry based intracellular cytokine–staining (ICS) assay, on peripheral blood mononuclear cells (PBMCs). At Day 29, total T cell counts were comparable among both treatment arms. GEMCOVAC®-OM showed relatively higher median of IL-2$^+$ CD4$^+$ T-Cells. Additionally, GEMCOVAC®-OM showed significantly higher spike-specific IFNγ$^+$CD8$^+$, TNFα$^+$CD8$^+$ as well as IL-2$^+$ CD8$^+$ T-cells compared to baseline. GEMCOVAC®-OM showed relatively better cross-reactive T-cell responses, specially CD8$^+$ T-cell responses as compared to GEMCOVAC®-19.

Immunogenicity of Phase III Clinical Trial

The Phase III study was a non-inferiority study that compared the safety and immunogenicity of GEMCOVAC®-OM (n = 3000) with COVISHIELD™ (n = 140). The immunogenicity cohort consisted of 271 participants from the GEMCOVCAC®-OM arm and 133 from the COVISHIELD™ arm.

PRNT$_{50}$ Assay: Comparison of live virus neutralization using PRNT$_{50}$ assay against the SARS-CoV-2 (omicron variant) at Day 29 was the primary endpoint of the Phase III study. GMT of neutralizing antibodies was higher in the GEMCOVAC®-OM group at Day 29 as compared to baseline. No increase in GMT occurred at Day 29 compared to baseline in the COVISHIELD group. LSGMR between GEMCOVAC®-OM and COVISHIELD™ calculated using ANCOVA was 1.58 (95% CI: 1.36; 1.84; $p < 0.0001$). Since the lower bound 95% CI of LSGMR is 1.36, GEMCOVAC®-OM is non-inferior (> 0.67 pre-defined margin) to COVISHIELD™. A post-hoc analysis showed that the lower bound 95% CI of LSGMR is above the WHO defined margin of superiority (> 1).

Sub-group analysis of participants who received COVAXIN® and COVISHIELD™ as their primary vaccination showed similar findings (Table 6).

Table 6. Neutralization by PRNT$_{50}$ assay against Omicron variant of SARS-CoV-2 in Phase III study

Time point	Primary vaccination COVAXIN®	Primary vaccination COVISHIELD™		Overall	
	GEMCOVAC-OM (n=78)	GEMCOVAC-OM (n=193)	COVISHIELD (n=133)	GEMCOVAC-OM (n=271)	COVISHIELD (n=133)
Baseline, GMT (95% CI)	511.02 (381.57, 684.39)	676.44 (561.39, 815.07)	775.38 (620.28, 969.26)	623.99 (533.38, 729.98)	775.38 (620.28, 969.26)
Day 29 GMT (95% CI)	1043.97 (869.73, 1253.11)	1123.47 (1003.89, 1257.29)	754.97 (631.55, 902.51)	1099.98 (1000.00, 1209.97)	754.97 (631.55, 902.51)

Seroconversion by $PRNT_{50}$: At Day 29, more subjects in the GEMCOVAC®-OM (39.5%) group achieved ≥2-fold rise in antibody titers as compared with subjects in the COVISHIELD™ (19.5%) group. The seroresponse rate difference between GEMCOVAC®-OM and COVISHIELD™ was 19.93 (95% CI: 10.57: 28.43) which was statistically significant ($p < 0.0001$). Since the lower bound 95% CI (10.57) of difference in seroconversion is > -10%, GEMCOVAC®-OM vaccine is non-inferior to COVISHIELD™.

Anti-Spike IgG Antibodies: Anti-spike IgG antibodies for GEMCOVAC®-OM was higher compared to COVISHIELD™ at Day 29 (Table 7). At Day 29, GMFR was greater in GEMCOVAC®-OM (7.25) compared to COVISHIELD™ (3.29). The LSGMR of IgG between GEMCOVAC®-OM and COVISHIELD™ was 2.15 (95% CI: 1.83; 2.52) and was statistically significant using ANCOVA with baseline titers as covariates ($p < 0.0001$). Since the lower bound of 95% CI of LSGMR is > 0.67, GEMCOVAC®-OM is non-inferior to COVISHIELD™.

Subgroup analysis on participants who received COVAXIN® and COVISHIELD™ showed similar findings (Table 7).

Table 7. Anti-spike IgG antibodies in the Phase III study

Time point	Primary vaccination COVAXIN®	Primary vaccination COVISHIELD™		Overall	
	GEMCOVAC-OM (N=78)	GEMCOVAC-OM (n=193)	COVISHIELD™ (N=133)	GEMCOVAC-OM (n=271)	COVISHIELD™ (N=133)
Baseline, GMT (95% CI)	28736.67 (22858.46, 36126.51)	41351.61 (36677.70, 46621.14)	39206.84 (34052.97, 45140.75)	37239.20 (33398.06, 41522.11)	39206.84 (34052.97, 45140.75)
Day 29, GMT (95% CI)	262673.63 (210500.59, 327777.88)	273022.44 (244074.15, 305404.13)	128916.02 (109548.25, 151707.95)	270002.72 (243972.39, 298810.33)	128916.02 (109548.25, 151707.95)

Seroconversion by Anti-Spike IgG Antibodies: More subjects in the GEMCOVAC®-OM group (252 [93.0%]) achieved ≥ 2-fold rise in IgG antibody titers as compared to subjects in the COVISHIELD™ group (102 [76.7%]) at Day 29. The difference in the seroresponse rate using the Meitinen-Nurminen method between GEMCOVAC®-OM and COVISHIELD™ was 16.30 (95% CI: 9.02, 24.64) and was statistically significant ($p < 0.0001$). Since the lower bound of 95% CI (9.02) is > -10%, GEMCOVAC®-OM vaccine is non-inferior to COVISHIELD™.

cPASS™ Neutralization Assay (Omicron Variant BA.1): Neutralizing antibodies (mean) were higher at Day 29 compared to baseline with both GEMCOVAC®-OM (Day 29: 94% vs Baseline: 68.1%, $p < 0.0001$) and COVISHIELD™ (Day 29: 94.3% vs 68.6%, $p < 0.0001$; Table 6). At Day 29, mean % change from baseline (standard error [SE]) in neutralizing antibodies was 25.7 (0.67) and 26.0 (0.96) in GEMCOVAC®-OM and COVISHIELD™, respectively. The difference of mean % change from baseline between GEMCOVAC®-OM and COVISHIELD™ was -0.2 (95% CI: -2.51; 2.09) and was not statistically significant.

Subgroup analysis on participants receiving COVAXIN® and COVISHIELD™ showed similar results (Table 8).

Table 8. Neutralization by cPASS™ in Phase III

Time point	Primary vaccination COVAXIN®	Primary vaccination COVISHIELD™		Overall	
	GEMCOVAC-OM (N=78)	GEMCOVAC-OM (n=193)	COVISHIELD™ (N=133)	GEMCOVAC-OM (n=271)	COVISHIELD™ (N=133)
Baseline, GMT (95% CI)	62.2 (56.18, 68.25)	70.5 (66.65, 74.29)	68.6 (64.13, 73.08)	68.1 (64.85, 71.33)	68.6 (64.13, 73.08)
Day 29, GMT (95% CI)	89.5 (85.89, 93.21)	95.8 (94.65, 96.90)	94.3 (92.16, 96.37)	94.0 (92.63, 95.33)	94.3 (92.16, 96.37)

Cellular Immune Responses: Both the vaccine arms showed numerically higher $IFN\gamma^+CD4^+$ T-cells at Day 29 from the respective baseline. At Day 29, GEMCOVAC®-OM group showed numerically higher $IFN\gamma^+CD4^+$ T-cells and significantly elevated $IL\text{-}2^+CD4^+$ T-cells as compared to the baseline. TNFα expressions in $CD4^+$ T-cells in the GEMCOVAC®-OM cohort at Day 29 showed statistically significant increase when compared to the COVISHIELD™ group. At Day 29, both the vaccinated arms showed significantly higher spike-specific $IFN\gamma^+$ $CD8^+$T-cells and marked increase in $TNF\alpha^+CD8^+$ T-cells. GEMCOVAC®-OM immunized subjects also showed significantly elevated IL-2 expressions in $CD8^+$ T-cells as compared to the baseline and as well as to the COVISHIELD™ vaccinated group. Spike-specific Th2 cytokines (IL-4 and IL-13) expressions in the T-cells from both the vaccinated cohorts were significantly lower when compared to the baseline

B cell responses to BA.1 and BA.5 were also assessed. At Day 29, GEMCOVAC®-OM immunized subject showed significantly elevated BA.1 specific B-cells as compared to the baseline as well as COVISHIELD™ booster vaccinated groups. GEMCOVAC®-OM immunized cohort showed significantly higher BA.5 reactive B-cells as compared to the COVISHIELD™ immunized cohort.

5.3 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

A GLP- compliant toxicity study to assess the skin irritation of GEMCOVAC®OM was conducted in New Zealand White rabbits. Four injection sites were identified on the skin of the back of three male and three female rabbits. GEMCOVAC®-OM was administered intradermally as a single dose on the back of the animals at two sites, whereas the CLNE control was similarly injected at one site. Intradermal injections were performed using a PharmaJet Needle-free Tropis® Injection system. The remaining one site served as an untreated (sham) control. The injection sites were evaluated at specified intervals till day-8 post injection for any evidence of local reaction. Erythema and oedema responses, if any, were graded according to the modified Draize scoring system. The animals were observed for mortality and signs of toxicity and their body weights were recorded. No deaths or clinical signs of systemic toxicity were observed in treated rabbits during the period of this study. Body weights of treated rabbits were not affected during the study period. No gross pathological changes were observed during necropsy in tissues/ organs of any of the rabbits in this study, when sacrificed on day-8. Observations of the skin revealed that intradermal injections in rabbits using the PharmaJet Tropis® device resulted in a reversible and a very slight, barely perceptible redness (grade 1) at the injection sites, not amounting to any significant irritation. Moreover, this minimal skin reaction, was comparable between the study vaccine and the CLNE control, and hence was attributed not to the 'antigenic' component of the test vaccine, but to the ingredients of the CLNE. It was found to be reversible in nature. GEMCOVAC®-OM was found to be safe, and well tolerated at the intradermal injection sites in rabbits.

Immunogenicity studies were conducted with GEMCOVAC®-OM in mice, rats and guinea pigs. The vaccine elicited robust humoral and cellular immune responses in different animal models.

7. DESCRIPTION

GEMCOVAC®-OM is a lyophilized powder that needs to be reconstituted with sterile water for injection. GEMCOVAC®-OM is supplied as a lyophilized powder in multiple dose vials of 5 doses.

For the 5 dose vial, draw 0.7 mL of Sterile Water for Injection and reconstitute the vial. Gently swirl the vial intermittently for approximately 180 seconds till all the lyophilized contents are dissolved and no particles are visible. The solution should be off white liquid free from any visible particles. Administer intradermal 0.1 mL of the reconstituted vaccine solution within 6 hours of reconstitution to the recipient. If not administered immediately, keep reconstituted vaccine back at +2ºC to +8ºC. Recipients who must be dosed on same day within 6 hours of reconstitution.

8. PHARMACEUTICAL PARTICULARS

One dose of vaccine (0.1 mL) contains: mRNA (10 µg), DOTAP (0.3 mg), Squalene (0.38 mg), Sorbitan Monostearate (0.37 mg), Polysorbate 80 (0.37 mg), Citric Acid Monohydrate (1.05 mg) and Sucrose (10 mg).

8.1 Incompatibilities

In the absence of incompatibility studies, the vaccine should not be mixed with any other medicinal products.

8.2 Shelf life

The expiry date of lyophilized vaccine is indicated on the label and outer pack. Once reconstituted, solution can be considered stable up to 6 hours when stored at +2ºC to +8ºC without opening flip off seal and rubber stopper. All reconstituted multi-dose vials of GEMCOVAC®-OM should be discarded at the end of immunization session or within six hours whichever comes first.

8.3 Packaging information

GEMCOVAC®-OM, Lyophilized mRNA Vaccine for Injection (COVID-19) Omicron variant is supplied in USP type I glass vial with Bromo-butyl rubber stopper and Flip-off Aluminium seal.

8.4 Storage and handling instructions

Store in a refrigerator (+2ºC to +8ºC). Do not freeze or shake the reconstituted solution. The vials should be used within 6 hours once opened. The vaccine should not be used beyond the expiry date as mentioned in the label.

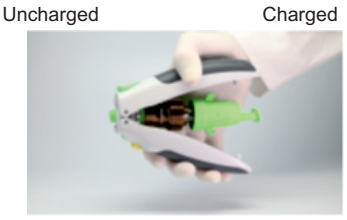
Intradermal Administration Procedure

- Reconstitute the vaccine vial with 0.7 mL of sterile water for Injection.
- Gently swirl the vial intermittently for approximately 180 seconds till all the lyophilized contents are dissolved and no particles are visible.

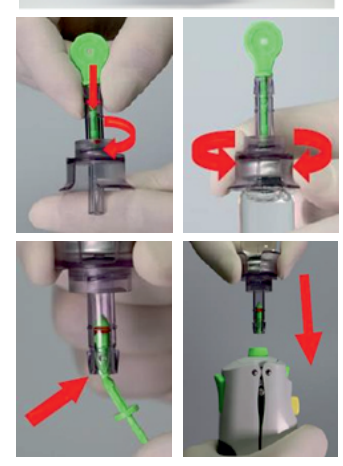
Uncharged

Charged

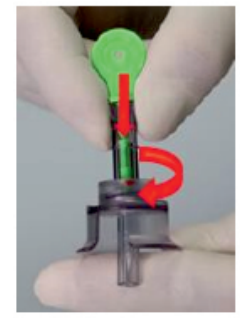
- Verify the injector is in the uncharged or charged state.



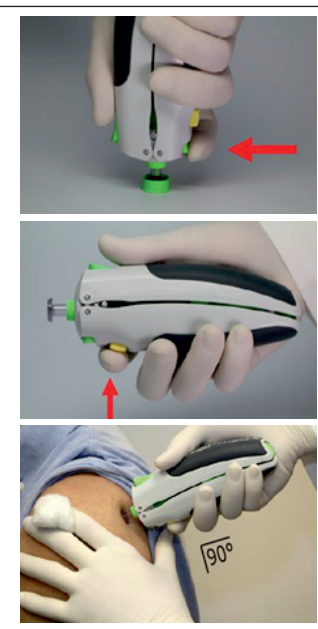
- Do not open the handle if it is charged. If uncharged, open the handle to prepare the Injector by pressing on the green button and then closing the handle.



- Remove the protective layer from the adapter and insert the syringe. Push down and clockwise to lock the syringe.
- Insert the adapter along with the syringe into the vial with a twisting motion.
- Invert the assembly and pull down the plunger to draw the vaccine till the red ring aligns with the fill line.
- Snap of the plunger.
- Insert the assembly into the charger until you hear a click.
- Invert the assembly and remove the syringe from the adapter by rotating counter clockwise.



- Close the adapter by inserting another syringe.



- While holding the yellow safety button, press the syringe perpendicular to the injection site.
- Inject by depressing the green activation button on the top of the injector.
- Remove the syringe by pressing the eject button.

9. PATIENT COUNSELLING INFORMATION

GEMCOVAC®-OM is a mRNA based vaccine which uses monovalent Omicron-adapted (BA.1) Spike (S)-protein of the SARS-CoV-2 virus as an antigen. The body is expected to develop an immune response post vaccination which will help in prevention of severe COVID-19 disease.
Inform the vaccine recipient of the potential benefits and risks of vaccination with GEMCOVAC®-OM. Advice the recipients to report any adverse event to their healthcare provider and by writing to Safety@gennova.co.in or calling the toll free number 18002090801.

10. DETAILS OF MANUFACTURER

GEMCOVAC®-OM is Manufactured and Marketed by:
Gennova Biopharmaceuticals Limited
Block 1, Plot No. P-1 & P-2,
ITBT Park, Phase II, MIDC,
Hinjawadi, Pune - 411 057, India.
® Registered Trade Mark Owned by
Gennova Biopharmaceuticals Limited

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License Number: PD/Vacc-6 Granted on 14.11.2006

12. DATE OF PREPARATION

8th May 2023

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