

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT:

COVAXIN[®] (Whole Virion Inactivated Coronavirus (SARS-CoV-2) Vaccine) is a white to off white, opalescent suspension free from extraneous particles containing 6 µg of Whole Virion, Inactivated (SARS-CoV-2) Antigen (strain NIV-2020-770).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each dose of 0.5mL contains:

Whole Virion, Inactivated Coronavirus (SARS-CoV-2) Antigen (Strain: NIV-2020-770) ... 6 µg

Aluminium Hydroxide Gel equivalent to Al⁺⁺⁺ 0.25 mg

TLR7/8 Agonist 15 µg

2-Phenoxyethanol 2.5 mg

Phosphate Buffered Saline q.s. to 0.5 mL

3. PHARMACEUTICAL FORM

Sterile suspension for injection.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indication

COVAXIN[®] is indicated for active immunization against SARS-CoV-2 Virus infection for age ≥18years. The vaccine is permitted for restricted use in emergency situation in public interest, under the provisions of New Drugs and Clinical Trials Rules, 2019, the Drugs & Cosmetics Act 1940.

4.2 Posology and method of administration.

COVAXIN[®] should be administered as two doses on Day 0 and Day 28.

Method of administration: Intramuscular injection (IM).

It is recommended that individuals who receive a first dose of **COVAXIN**[®] complete the vaccination course with **COVAXIN**[®]

4.3 Contraindications

- Hypersensitivity to any constituents of the vaccine.

4.4 Special warnings 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.
- Concurrent illness: As with other vaccines, administration of COVAXIN[®] should be postponed in individuals suffering from an acute severe febrile illness/acute infection.
- Thrombocytopenia and coagulation disorders: As with other intramuscular injections, COVAXIN[®] should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.
- 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. Immunocompromised individuals may have relatively weaker immune response to the vaccine regimen.
- Paediatric population: Clinical trials for the evaluation of Safety and Efficacy of COVAXIN[®] in children and adolescents (aged below 18 years) are ongoing. Limited data are available
- Interchangeability: No data are available on the use of COVAXIN[®] in persons that have previously received partial vaccine series with another COVID-19 vaccine.
- Vaccinees should remain under medical supervision for at least 30 minutes after vaccination.

Before administration, the vaccine vial should be shaken well to obtain a uniform, whitish translucent suspension. Vial should be visually checked for the presence of any particulate matter or other colouration, if any, prior to its administration. If in doubt, do not use the contents of the vial. COVAXIN[®] should not be mixed with other vaccines.

4.5 Interaction with other medicinal products.

No interaction studies have been performed. Concomitant administrations of COVAXIN[®] with other medicinal products have not been studied.

4.6 Pregnancy and Lactation

Safety, efficacy, and immunogenicity have not been established in pregnant women and nursing mothers, though vaccine is permitted in lactating mothers. Available data on COVAXIN[®] Vaccine administered to pregnant women are insufficient to inform vaccine associated risks in pregnancy.

The use of COVAXIN[®] in pregnant women is recommended only if the benefits of vaccination to the pregnant woman 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 co-morbidities

that add to their risk of severe disease), the likely benefits of vaccination in the local epidemiologic context, and the current limitations of the safety data in pregnant women.

4.7 Effects on ability to drive and use machines

No studies on the effect of COVAXIN[®] on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trial Experience

Safety of the COVAXIN[®] vaccine was evaluated in the ongoing Phase 1, Phase 2 and Phase 3 studies.

Phase 1 clinical trial

The Phase 1 clinical trial was conducted in India in 375 healthy adult volunteers. The first 50 participants enrolled were monitored for 7 days after vaccination, and on the basis of the independent data safety monitoring board review of masked safety data, the trial was allowed to continue with enrolment of the remaining participants into all groups. Participants were randomly assigned to receive either one of three vaccine formulations (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) or an Algel only control vaccine group. After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10.5–26.1) participants in the 3 µg with Algel-IMDG group, 21 (21%; 13.8–30.5) in the 6 µg with Algel-IMDG group, 14 (14%; 8.1–22.7) in the 6 µg with Algel group, and ten (10%; 6.9–23.6) in the Algel-only group. The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (nine [2%]), and nausea or vomiting (seven [2%]). All solicited adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose. One serious adverse event of viral pneumonitis was reported in the 6 µg with Algel group, unrelated to the vaccine

Phase 2 clinical trial

The Phase 2 clinical trial was conducted in India in 380 adolescents and healthy adult volunteers. Participants were randomly assigned (1:1) to receive either 3 µg with Algel-IMDG or 6 µg with Algel-IMDG. After both doses, the most common solicited adverse events were injection site pain, reported in five (2.6% [95% CI 0.9–6.0]) of 190 participants in the 3 µg with Algel-IMDG group and six (3.2% [1.2–6.8]) of 190 participants in the 6 µg with Algel-IMDG group. Most adverse events were mild (69 [89%] of 78 participants) and resolved within 24 h of onset. At 7 days after the second dose, solicited local and systemic adverse reactions were reported in 38 (20.0% [14.7–26.5]) of 190 participants in the 3 µg with Algel-IMDG group and 40 (21.1% [15.6–27.7]) of 190 participants in the 6 µg with Algel-IMDG group. No association between the dose of vaccine and the number of adverse events was observed. The most common adverse event in the phase 2 trial

was pain at the injection site, followed by headache, fatigue, and fever. No severe or life-threatening (ie, grade 4 and 5) solicited adverse events were reported. No significant differences in safety were observed between the two groups.

No significant difference in the proportion of participants who had a solicited local or systemic adverse reaction in the 3 µg with Algel-IMDG group (38 [20.0%; 95% CI 14.7–26.5] of 190) and the 6 µg with Algel-IMDG group (40 [21.1%; 15.5–27.5] of 190) was observed on days 0–7 and days 28–35; no serious adverse events were reported in the study.

Phase 3 clinical Trial

Safety

BBV152 demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age, including adults ≥60 years of age (including those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19). In line with other inactivated vaccines, hypersensitivity reactions following immunization with BBV152 were rare and usually nonserious. Severe allergic (anaphylactic) reactions have not been reported in BBV152 clinical studies to date.

A total of 5959 adverse events (AEs) were reported by 3194 subjects, with a comparable proportion (12.4%) of subjects experiencing at least one AE in the BBV152 and placebo groups. The AEs reported in the BBV152 group were mild (11.2%), moderate (0.8%), or severe (0.3%) and were comparable to the placebo group (mild [10.8%], moderate [1.1%], and severe [0.4%]). A total of 106 serious adverse events (SAEs) were reported by 99 subjects in the study; 40 events in the BBV152 group and 66 events in the placebo group. Overall, the placebo group (60 [0.47%] subjects) had a higher incidence of SAEs as compared to the BBV152 group (39 [0.30%] subjects). Only one SAE (Immune thrombocytopenia) under the System Organ Class of ‘blood and lymphatic disorders’ was considered related to BBV152 administration. There were 15 deaths in the study, none of which were considered by the investigators to be related to BBV152 or placebo; 6 deaths were reported to be related to COVID-19. In the BBV152 group, there were 5 deaths all due to causes unrelated to vaccination. These causes included haemorrhagic stroke, metastatic ovarian cancer, cardiac arrest, COVID-19 and sudden cardiac arrest/intracranial haemorrhage (unconfirmed). Ten deaths in the placebo group were due to unrelated conditions and included cardiopulmonary failure, cardiac arrest probably due to acute coronary syndrome and with underlying hypertension, COVID 19 (5 subjects), 1 death with unknown cause and symptoms of headache, and 2 deaths which remain to be determined.

No anaphylactic events were reported.

Approximately 9% of subjects experienced at least one solicited AE within 7 days post vaccination; overall incidence rates of solicited AEs were lower after Dose 2 (4.3% subjects) than Dose 1 (5.9% subjects) and tended to be slightly higher in the BBV152 group than the placebo group. Among the local or systemic solicited AEs, only

local injection pain was reported with an incidence >1% after either dose and an overall combined incidence of about 4% across groups. Similar proportions of subjects in BBV152 (3.04%) and placebo (2.78%) groups reported local pain after the first dose, falling to 1.81% and 1.62% subjects after the second dose, respectively. Other frequently reported local AEs included injection site erythema, injection site induration, and injection site swelling, reported by < 0.3% of subjects in any group after either dose.

Solicited systemic AE were reported less frequently in 2.57% and 1.92% subjects after Dose 1; and in 1.8% and 1.6% subjects after Dose 2 in the BBV152 and placebo groups, respectively. The most frequent solicited systemic AE overall was headache, followed by pyrexia, fatigue and myalgia; all with incidences below 1% in both groups. A total of 767 unsolicited AEs were reported from 450 subjects; 1.76% in the BBV152 group and 1.74% in the placebo group. All unsolicited AEs occurred in <1% of subjects with a comparable incidence between BBV152 and placebo groups; the most common events were pyrexia, cough, headache, and oropharyngeal pain. Immediate AEs within 30 minutes were observed in only 0.1 % of subjects post Dose 1 and 0.04% of subjects post Dose 2. A higher number of immediate AEs within 30 minutes post-dose were observed in the placebo group (29 events, 23 subjects) as compared to the BBV152 group (14 events, 12 subjects); most of these immediate AEs occurred post Dose 1. The proportion of subjects experiencing any MAAEs and AESIs were comparable between the BBV152 and placebo groups. Adverse events led to discontinuation of study intervention in overall 19 subjects –13 subjects in the BBV152 group and 6 subjects in the placebo group. Overall, BBV152 exhibited a good reactogenicity profile with similar rates of solicited, unsolicited, and serious adverse events, and AESIs in BBV152 and placebo groups.

Based on a safety review conducted by the National AEFI (Adverse Event Following Immunization) Committee to the Ministry of Health & Family Welfare, after administration of 6,784,562 doses of BBV152, there were no potential thromboembolic events reported through the CO-WIN platform.

Data on medically attended adverse events (MAAEs), serious adverse events (SAEs) and deaths were collected from all 25,798 participants who received a study vaccination and will continue to be collected for a total of 1 year.

4.9 Immune Response and Efficacy

COVID-19 disease is caused due to SARS-CoV-2 virus infection.

Immunogenicity studies in humans (Phase 1 and 2)

The Phase 1 trial showed seroconversion rates (%) were 91.9% in the 6 mcg with Algel-IMDG post dose 2. Post 28 days second-dose Geometric mean titres (GMTs) were 66.4 [95% CI 53.4–82.4] in the 6 mcg Algel-IMDG group based on MNT₅₀. CD4+ and CD8+ T-cell responses were detected in a subset of 8 participants from 6 mcg Algel-IMDG groups. Additionally, IgG using

ELISA assays were determined against spike (S1) glycoprotein, receptor-binding domain, and nucleocapsid protein of SARS-CoV-2 increased rapidly after the administration of the two-dose regimen. The mean isotyping ratios (IgG1/IgG4) were greater than 1 for the vaccinated group, which was indicative of a Th1 bias in immune response.

Three months after dose two receipt, follow up serum samples were collected from the Phase 1 study participants. In the 6mcg group, GMTs (MNT₅₀) at day 104 were 69.5 [95% CI 53.7–90.0]. Seroconversion based on MNT₅₀ was reported in 76 (81.1% [95% CI 71.4–88.1]) participants in the 6 mcg with Algel-IMDG group. This suggests that GMTs were maintained after 28 days post dose two and 104 days. T-cell memory responses were also evaluated and found to be persistent among phase 1 vaccine recipients.

In the phase 2 trial, for the 6mcg Algel-IMDG group similar results were found with GMTs plaque reduction neutralization test (PRNT₅₀) at day 0 of 0.10 [95% CI 0.09-0.11], which then increased to 197.0 (95% CI 155.6–249.4) at day 56. Seroconversion based on PRNT₅₀ at day 56 was reported in 174 (98.3% [95% CI 95.1–99.7]) of 177 participants. GMTs (MNT₅₀) at day 56 were 160.1 (95% CI 135.8–188.8). Seroconversion based on MNT₅₀ at day 56 was reported in 171 (96.6% [95% CI 92.6–98.5]) of 177 participants. IgG antibody titres (GMTs) to all epitopes (spike glycoprotein, receptor-binding domain, and nucleocapsid protein) were detected after the administration of the vaccine. The Th1/Th2 cytokine ratio indicated bias to a Th1 cell response at day 42.

Immunogenicity studies against Variants of Concern:

Neutralizing antibody titres (PRNT₅₀) of sera collected (4 weeks after the second dose) from 38 vaccine recipients, who received the BBV152 vaccine candidate in the Phase II trial (no evidence of previous SARS-CoV-2 infection) were evaluated to determine the immunogenicity of the BBV152 vaccine candidate against of the three different virus strains including VOC Alpha (B.1.1.7). A representative set of 20 serum samples of vaccine recipients were also tested to serve as comparison samples. Using PRNT₅₀ values from these groups showed a non-significant difference ($P > 0.05$) in neutralization between the three tested strains.

Further immunogenicity studies were done as described as follows: using sera of 28 BBV152 vaccinated individuals (no evidence of previous SARS-CoV-2 infection), collected during the phase II clinical trial and sera samples collected from COVID-19 recovered individuals (n=17) PRNT₅₀ testing was conducted. This demonstrated that neutralizing capacity against Delta Variants of Concern (VOC) (B.1.617.1) was similar from sera of vaccinated individuals and that of recovered cases. Another study was done to determine the IgG immune response and neutralizing activity of 19 convalescent sera specimens obtained from recovered cases of COVID-19 and confirmed for VOC Alpha (B.1.1.7, [n = 2]), Beta (B.1.351 [n = 2]), B.1.1.28.2 (n = 2), B1 lineage (n = 13) (15–113 days post positive test). The data were compared with sera from 42 participants immunized with BBV152 as part of phase II clinical trial (2 months post the second dose). This study found a high levels of cross-neutralization in sera collected from variant infected

individuals compared to those vaccinated with BBV152. One other study was reported where the neutralization antibodies in sera collected from COVID-19 recovered cases (n=20) and vaccinees with two doses of BBV152 (n=17) against VOC Beta (B.1.351) and VOC Delta (B.1.617.2) compared. While there was a reduction in neutralization titers in sera of COVID-19 recovered cases (3.3-fold and 4.6-fold) and BBV152 vaccinees (3.0 and 2.7 fold) against VOC Beta (B.1.351) and VOC Delta (B.1.617.2) respectively, there was cross neutralization against these two VOCs.

Phase 3 clinical trial

Efficacy

The phase 3 study is an ongoing, multi-center, randomized, double-blind, placebo-controlled in India that assesses the efficacy, safety, and immunogenicity of a two-dose regimen of BBV152 for the prevention of symptomatic COVID-19 in adults aged 18 years and older. The study is being conducted in 25 different sites in India. A total of 25,798 participants were randomized of whom 24,419 were vaccinated with either two doses of BBV152 or placebo. The study included adults over 18 years of age who were healthy or had stable medical conditions. It was relatively well-balanced among subgroups with regard to age, comorbidities and sex. The study enrolled participants at 25 sites with the ability to conduct RT PCR and serology for COVID-19, from November 16, 2020 to January 7, 2021. The time of study enrolment coincided with the emergence of new SARS-CoV-2 variants, some participants within the study included these variants of concern. Efficacy results were based on the primary analysis, which included 12,879 participants who received the vaccine and 12,874 participants who received placebo, as first dose. This interim analysis included data up to May 17, 2021 and included a median of 146 days of safety data available after the first dose and a median of 99 days of efficacy follow up two weeks after a second dose.

At the time of the reported per-protocol analysis, 130 laboratory-confirmed primary endpoint cases were observed with an onset at least 14 days after vaccination with dose 2. Of these cases, 24 occurred in the vaccinated group and 106 (occurred in the placebo group). The vaccine efficacy was found to be 77.8% (95% CI: 65.2 – 86.4). Further analysis was conducted to look at secondary endpoints including severe disease. In this analysis a total of 16 participants (1 vaccine recipient, 15 placebo recipients) yielding a vaccine efficacy of 93.4% (95% CI: 57.1–99.8) against severe disease.

In the analysis of confirmed symptomatic COVID-19 cases a total of 79 variants were reported from 16,973 samples, 18 in the vaccine and 61 in the placebo group. Among 50 Delta (B.1.617.2) positive-confirmed cases, 13 and 37 participants were in the vaccine and placebo arms, resulting in vaccine efficacy of 65.2% (95% CI: 33.1–83.0).

The study design also included routine monthly PCR testing, therefore, the investigators were able to determine efficacy against asymptomatic COVID-19 was 63.6% (95% CI: 29.0–82.4), with a total of 46 asymptomatic cases (13 in vaccine recipients and 33 in placebo recipients) (n = 6289).

Immunogenicity:

The GMT values for SARS-CoV-2 specific nAb were comparable across all groups at Day 0. At Day 56, in the groups who received BBV152 Lots 1, 2, 3, or placebo, the GMTs of SARS-CoV-2 nAb were 130.3 [95% CI: 105.8 – 160.4], 121.2 [95% CI: 97.6 – 150.5], 125.4 [95% CI: 101.3 – 155.1], and 13.7 [95% CI: 10.7 – 17.4], respectively. The point estimate of GMT [95% CIs] ratios for SARS-CoV-2 specific neutralising antibody between all three pairs of lots were consistently similar: 1.075 [0.798 – 1.449] in Lot 1 vs. Lot 2; 1.039 [0.772 – 1.398] in Lot 1 vs. Lot 3; and 0.966 [0.714 – 1.308] in Lot 2 vs. Lot 3. All the 95% CIs for the GMT ratios were contained within [0.5 – 2.0] for INDIA and [0.67 – 1.5] for US-FDA, thus, meeting the predefined criterion for consistent immune response across lots.

4.10 Overdose:

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

COVID-19 disease is caused due to SARS-CoV-2 virus infection. **COVAXIN[®]** has been studied in an ongoing Phase 1 and 2 clinical studies for safety and immunogenicity and found to be safe and immunogenic. In the ongoing Phase 3 trial, **COVAXIN[®]** has been shown to prevent COVID-19 following 2 doses of vaccine given 4 weeks apart based on the interim analysis showing vaccine efficacy to be 77.8%. The duration of protection against COVID-19 is currently unknown.

5.2 Pharmacokinetic properties:

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

All the formulations were tested for immunogenicity in mice, rats, and rabbits. Mice, rats, and rabbits were vaccinated on days 0, 7, and 14 (n+1 doses). Further, these formulations are tested for immunogenicity, safety, and protective efficacy in the Syrian Hamster challenge model and Non-Human Primates (Rhesus macaque) challenge model. The Hamsters were vaccinated on Days 0, 14, and 35 (n+1 doses), the live SARS-CoV-2 virus was challenged through the intranasal route on Day 50. Likewise, the Rhesus macaques were vaccinated on Days 0 and 14, and the live SARS-CoV-2 virus was challenged through intranasal and intratracheal routes on Day 28. All the formulations were found to be safe, immunogenic, and provided effective protection to both the upper and lower respiratory tract.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Aluminium hydroxide gel, TLR7/8 Agonist, 2-Phenoxyethanol, Phosphate Buffered Saline

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of **COVAXIN**[®] is indicated on the label and carton of the vaccine. Do not use the vaccine after the expiration date shown on the label and carton of the vaccine.

6.4 Special precautions for storage

Store at +2° to +8 °C, do not freeze. Discard if frozen.

Shake well before use. Keep out of reach of children. Protect from light.

Store vials in the original carton till the vial is used.

7. PRESENTATION

COVAXIN[®] is presented in USP type 1 glass.

Single dose vial - 0.5mL

Multi dose vial - 2.5mL (5 dose)

Multi dose vial - 5.0mL (10 dose)

Multi dose vial - 10.0mL (20 dose)

Opened vials may be used in subsequent immunization session for up to a maximum of 28 days provided that all of the following conditions are met (as described in the WHO policy statement: Multi-dose vial Policy (MDVP) Revision 2014 WHO/IVB/14.07).

- The expiry date of the vaccine has not passed.
- The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO
- The vaccine vial has been, and will continue to be, stored at +2°C to +8°C
- The vaccines are stored under appropriate cold chain conditions.
- The vaccine vial septum has not been submerged in water.
- The aseptic technique has been used to withdraw all doses.
- The vaccine vial monitor (VVM), if attached, has not reached the discard point.

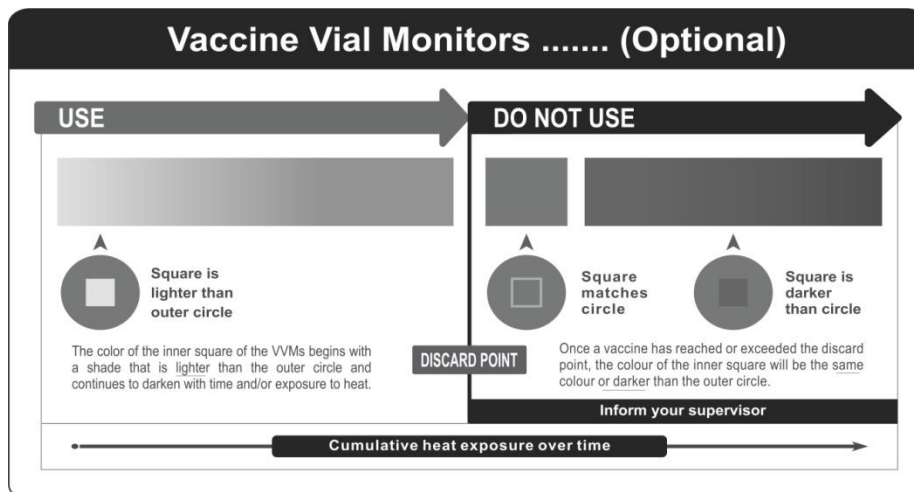
An opened vial must be discarded immediately if any of the following conditions apply.

- Sterile procedures have not been fully observed.
- There is even a suspicion that the opened vial has been contaminated or
- There is visible evidence of contamination, such as a change in the appearance of floating particles.
- If the vaccine vial is frozen or breakage in the continuity of the vials (crack/leaks).

8. THE VACCINE VIAL MONITOR (OPTIONAL)

Presentation available with or without vaccine vial monitor

Vaccine Vial Monitors (VVM7) dot is on the seal of 0.5mL vials and VVM7 is part of the label on 2.5mL, 5mL & 10mL COVAXIN[®] vials supplied through Bharat Biotech. VVM7 are supplied by TEMPTIME Corporation, USA. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end-user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.



The interpretation of the VVM7 is simple: Focus on the central square; its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, the vial should be discarded.

9. MARKETING AUTHORIZATION NUMBER(S)

MF/BIO/21/000002, dated 3rd January, 2021.

10. MARKETING AUTHORIZATION HOLDER:



Bharat Biotech International Limited
Genome Valley, Hyderabad, TS - 500078, India
T: +91 40 4645 4545 www.bharatbiotech.com

For complaints and suggestions about the product and any adverse event,
Please email to feedback@bharatbiotech.com Or call on Toll-free number: 1800 102 2245*