SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT:

ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant) is a colorless to pinkish liquid, free from extraneous particles, containing NLT $5x10^{10}$ virus particles per mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Dose of 0.5 mL, total of 8 drops contains:

ChAd36-SARS-CoV-S COVID-19 virus (recombinant)	NLT $5x10^{10}$ particles per mL
Tris (pH 7.4)	20 mM
Sodium Chloride	25 mM
Magnesium Chloride	2 mM
Glycerol	NLT 2.5 %
Polysorbate- 80	0.1%

For excipients see section 6.1.

3. PHARMACEUTICAL FORM:

Vaccine (Liquid)

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant) is indicated for active immunization against Coronavirus infection (SARS-CoV-2) COVID-19.

iNCOVACC® is indicated for active immunization against SARS-CoV-2 virus infection for age ≥ 18 years for restricted use in emergency situation in public interest.

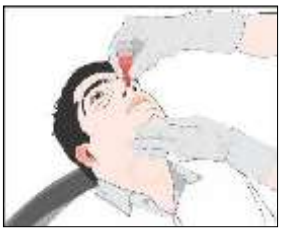
4.2 Posology and method of administration.

iNCOVACC® is an Adenoviral vector-based (expressing a stabilized spike protein) SARS-CoV-2 vaccine for nasal administration only.

iNCOVACC® vaccination course consists of TWO separate doses of 0.5mL (8 drops, 4 drops in each nostril). The second dose should be administered after 28 days (4 weeks from the first dose).

Method of administration:

1. Blow nose gently to clear.
2. Tilt head back as far as comfortable (See diagram).
3. Insert dropper a little way into nostril and squeeze bulb gently to release 4 drops into nostril and keep head back for 30 seconds.
4. Repeat in another nostril.



Drops in Right Nostril

In case **iNCOVACC®** partially or completely does not enter the nostril, you may re-administer into the same nostril. In case the recipient prematurely gets up, and the **iNCOVACC®** liquid is seen running from any nostril, you may re-administer to that nostril.

Once opened, Multi-Dose vials should be used within 6 hours and stored at 2 to 8ºC between administrations. Post 6 hours after opening, the vials should be discarded.

iNCOVACC® is presented as a two dose presentation per vial and for nasal use only. Care should be taken not to contaminate the dropper of the vaccine while administration. Post administration of 8 drops to the recipient, the dropper should be discarded and new dropper should be affixed prior administration to the next recipient. In case, the vaccine is not used immediately for administration to the second recipient, the open vial should be closed with rubber stopper. A new dropper should be placed for the administration of vaccine to the second recipient. The vaccine should not be used beyond 6 hours after the vial is opened.

To facilitate the traceability of the vaccine, the name and the batch number of the administered product must be recorded for each recipient.

4.3 Contraindications

Hypersensitivity to any constituents of the vaccine.

4.4 Special warnings and precautions for use

- Do not administer intramuscularly, intravenously, intradermally, or subcutaneously.
- Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization. Vaccinees should remain under medical supervision for at least 30 minutes after vaccination.
- Concurrent illness: As with other vaccines, administration of iNCOVACC® should be postponed in individuals suffering from an acute severe febrile illness/acute infection.
- Thrombocytopenia and coagulation disorders**:** iNCOVACC® should be given with caution to individuals with thrombocytopenia, 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. Immunocompromised individuals may have relatively weaker immune response to the vaccine regimen.

- **Paediatric population:** Data are not available for the use of **iNCOVACC®** in paediatric population.

4.5 Interaction with other medicinal products.

No interaction studies have been performed.

4.6 Pregnancy and Lactation

Not applicable

4.7 Effects on ability to drive and use machine

No studies on the effect of **iNCOVACC®** on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trial Experience (Safety)

Safety of the iNCOVACC® vaccine was evaluated in the Phase 1, Phase 2 and Phase 3 trials of adults age ≥18 years.

Phase 1 clinical trial

The phase 1 study was conducted in India with a total of 175 subjects, 70 in group A (Single dose), 70 in group B (Double dose) and 35 in group C (Placebo). Among 70 subjects in group A, 57 (81.43%) were males and 13 (18.57%) were females. In group B, among 70 subjects, 57 (81.43%) were males and 13 (18.57%) were females. In group C, among 35 subjects, 30 (85.71%) were males and 5 (14.29%) were females.

	Total number of subject N= 175					
	Group A (Single dose N=70)		Group B (double dose N=70)		Group C (placebo N=35)	
	Male	female	Male	female	male	female
	57 (81.43%)	13 (18.57%)	57 (81.43%)	13 (18.57%)	30 (85.71%)	5 (14.29%)
Total Solicited Adverse events reported 8	Total 3 (4.29%) events were reported of which 2 events Head ache, 1 event of Fever		Total 5 (7.14%) events were reported of which 3 events Fever, 2 events Sneezing		No adverse events	

A total of 8 solicited adverse events were reported during the study. 3 adverse events were reported from group A, 5 adverse events were reported from group B and no adverse events were reported from group C.

In group A, 3 solicited adverse events (2 events of headache and 1 event of Fever) were reported in 3 subjects (4.29%). In group B, 5 solicited adverse events (3 events of Fever and 2 event of Sneezing) were reported in 5 subjects (7.14%).
No serious adverse event was reported in the study.

Phase 2 clinical trial
A Phase 2, Randomized, Double Blinded, Multi-centric Study to evaluate the Immunogenicity, Reactogenicity and Safety of an Intranasal ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant) was conducted in 200 Healthy Volunteers of ages 18 to 60. A total of 200 subjects participated in the study, of which 148 (74.00%) were male and 52 (26.0%) were female. Among 160 subjects in vaccine, 118 (73.75%) were male and 42 (26.25%) were females. In placebo group, among 40 subjects, 30 (75.00%) were males and 10 (25.00%) were females.

Groups	**Total number of subjects N=200 age group between 18 to 60**		
	Male	Female	**Total Solicited Adverse event reported 6**
Group 1(N=160) Vaccine	118 (73.75%)	42 (26.25%)	Total 5 (3.12%) event were reported of which 2 events of running nose, 3 event of Headache
Group 2 (N= 40) Placebo	30 (75.00%)	10 (25.00%)	1 event of headache (2.5%)

iNCOVACC® is well tolerated in both the treatment groups. A total of 6 solicited adverse events were reported during the study. 5 solicited adverse events were reported in group-1 (2 events of running nose and 3 event of Headache) were reported in 5 subjects (3.12%). 1 adverse event (Headache) was reported in 1 subject (2.5%) in group-2. All 6 adverse events were mild in severity and resolved. Majority of the adverse events, within 1 day. These 6 adverse events were reported in 6 volunteers, which is about 3% of the total volunteers.
No serious adverse event was reported in the study.

Phase 3 clinical trial
A Phase 3 randomized open label multi-centric study to compare immunogenicity and safety of **iNCOVACC®** with COVAXIN®, and to assess Lot to Lot Consistency of **iNCOVACC®** in Healthy Volunteers is ongoing in 3160 subjects of 18 years and above. The data is analyzed till day 90 for a total of 3141 subjects. Percentage of male subjects enrolled in the study are 69.24% and the female subjects are 30.76%.

Total subjects	3160 subjects	
Data analyzed till day 90	3141 subjects	
	Male	69.24%
	female	30.76%.
Total 248 Adverse event till day 90	**BBV154**	**COVAXIN**
	197 subjects	51 subjects
Solicited local adverse events	3.28% running nose, sneezing, nasal congestion, nasal pain, sore throat, lacrimation.	21.73% Injection site pain, injection site swelling and injection site redness.
Common Solicited systemic events reported	Fever, Headache, Myalgia, Fatigue, Nausea and Vomiting.	Fever, Headache, Nausea
No Serious Adverse Events were seen in both groups		

All the subjects in both the groups were followed up till day 90.
A total of 248 adverse events, 197 in BBV154 group and 51 in COVAXIN group were reported in the study till day 90.
Solicited local adverse events reported in a total of 3.28% of subjects in BBV154 group and in a total of 21.73% of subjects in COVAXIN group. The local events were different for BBV154 and BBV152.
Common Solicited local events seen in BBV154 are running nose, sneezing, nasal congestion, nasal pain and sore throat.

Common solicited local events seen in COVAXIN are injection site pain, injection site swelling and injection site redness.

Common Solicited systemic events reported in both the groups were Fever, Nausea and Vomiting.
All these common events were reported in a very less percentage of subjects in BBV154 group compared to BBV152 group.
No SAEs were observed in both the groups (BBV152 and BBV154).
No cases of Covid-19, Thrombocytopenia, Guillian Barre syndrome, Myocarditis were reported in the study.

The safety profile was excellent in BBV154 group as compared to BBV152 group.

4.9 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. **iNCOVACC®** has been studied in a Phase 1 and 2 and an ongoing Phase 3 clinical studies for safety and immunogenicity and found to be safe and immunogenic.

Immune Response and Efficacy

Immunogenicity studies in humans:

Phase 1 clinical trial

In Phase 1, GMTs using MNT_{50} were calculated for all the three Arms. This was calculated for baseline Day 0 titres and post vaccination Day 28 and 42.

At baseline, geometric mean titres were 17.97 (95% CI 11.73, 27.51), 16.75 (95 % CI 11.6, 24.19) and 15.05 (95% CI 9.84, 23.02) in group A, B and C respectively. On Day 28, geometric mean titres were 47.9 (95% CI 30.44, 75.38), 44.01 (95 % CI 28.3, 68.44) and 17.36 (95% CI 10.68, 28.21) in group A, B and C respectively. On Day 42, geometric mean titres were 65.58 (95% CI 41.27, 97.94), 150.7 (95 % CI 108.6, 209.1) and 23.89 (95% CI 13.44, 42.46) in group A, B and C respectively.

Days	**Statistics**	**Group A**	**Group B**	**Group C**
Day 0	GMT 95 % CI	17.97 (11.73,27.51)	16.75 (11.6, 24.19)	15.05 (9.84, 23.02)
Day 28	GMT 95 % CI	47.9 (30.44,75.38)	44.01 (28.3, 68.44)	17.36 (10.68, 28.21)
Day 42	GMT 95 % CI	65.58 (41.27,97.94)	150.7 (108.6, 209.1)	23.89 (13.44, 42.46)

Phase 2 clinical trial

In Phase 2, the GMTs of $PRNT_{50}$ at day 0 were **3.1** (95% CI 1.65,5.67) and at day 42 were **286.8 (95% CI** 190.32,432.09) for BBV154 and **3.7 (95%CI** 1.01,13.73) at day 0 and **47.1 (95% CI** 12.34,179.58) at day 42 for placebo.

Drug	**Statistics**	**Day 0**	**Day 42**
BBV154	GMT 95 % CI	3.1 (1.65,5.67)	286.8 (32,432.09)
placebo	GMT	3.7	47.1

	95 % CI	(1.01,13.73)	12.34,179.58

Phase 3 clinical trial

In Phase 3 study, the GMTs of $PRNT_{50}$ at day 0 were 26.1 (95% 18.7,36.6) and at day 42 were 768.5 **(95% CI** 665.1,888.0) for BBV154 and 37.0 **(95%CI** 21.0,65.4) at day 0 and at day 42, 531.0 **(95% CI** 425.9,662.1) for BBV152/COVAXIN®, as comparator.

Drug	**Statistics**	**Day 0**	**Day 42**
BBV154	GMT 95 % CI	26.1 (18.7,36.6)	768.5 (665.1,888.0)
BBV152/ COVAXIN®	GMT 95 % CI	37.0 (21.0,65.4)	531.0 (425.9,662.1)

Effectiveness against SARS-CoV-2 Variants

BBV154 nasal vaccine has been evaluated and shown satisfactory immune response against several variants of such as Delta, Beta and Omicron including the recent variant BA.5. Cell mediated immune response, both T and B cell phenotype distribution is evaluated against SARS-CoV-2 variants including omicron variants found the response is persistent across variants.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines

5.3 Preclinical safety data

Safety and immunogenicity in Mice, Rats, Hamsters and Rabbits

Repeated dose intranasal immunogenicity and safety study with BBV154 in laboratory animals (BALB/c mice, Swiss Albino mice, Wister rats, Syrian Hamsters and New Zealand Rabbits) was conducted based on the New Drugs and Clinical Trails Rules, 2019 and WHO guidelines on Nonclinical Evaluation of Vaccines.

Treatment with BBV154 did not show treatment related changes in clinical signs, body weights, feed consumption, body temperature, clinical pathology, terminal fasting body weights, organ weights and gross pathology in both sexes. There was no treatment related microscopic findings observed in animals treated with BBV154.

No mortality was observed throughout the study period. No clinical signs of toxicity were observed in all the treated animals.

No adverse effect on body weight and body weight gain was observed for treated animals. No significant change in the body temperature of the all the treated animals. No adverse effects on feed consumption were noted for all the treated animals.

Local reactogenicity was assessed Prior to study, on day of each dosing and followed by 24 hours as per Draize scoring system. No skins reactions were observed.

There were no treatment related changes observed in clinical pathology parameters, terminal fasting body weights and organ weights in any of the groups in both sexes.

Animals immunized through intranasal route with BBV154, at a given antigen concentrations found to be immunogenic, eliciting high levels of IgG and IgA antibodies specific to SARS-CoV-2 S1 antigen. High Neutralization antibody titers were observed in BBV154 immune serum.

In conclusion, treatment with BBV154 even at high dose (5×10^{11} VP/animal) did not produce any treatment related changes when administered with full Human Single Dose (HSD) of multiple doses (n+1).

Challenge Studies of ChAd36-SARS-CoV-2-S Carried out at Washington University.

Introduction: ChAd36-SARS-CoV-2-S is an adenoviral based SARS-CoV-2 intranasal vaccine (ChAd36-SARS-CoV-2-S) expressing a prefusion stabilized spike (S) protein developed by Michael Diamond's group (Washington University, Saint Louis, USA).

Brief summary of challenge studies

Challenge studies were performed in three different animal models, K18-hACE2 transgenic mice, Syrian hamster and non-human primates.

(i) K18-hACE2 transgenic mice: Mice were immunized with ChAd-SARS-CoV-2-S, in two different routes. Both, Intranasal or intramuscular administration of ChAd-SARS-CoV-2-S, prevents SARS-CoV-2 lung infection and pneumonia in mice. In particular, intranasal delivered ChAd-SARS-CoV-2-S uniquely prevents both upper and lower respiratory tract infections, potentially protecting against SARS-CoV-2 infection and transmission (*Hassan et al. 2020*).

(ii) Syrian Hamsters: Similarly, intranasal administration of ChAd36-SARS-CoV-2-S in Syrian hamster showed superiority over intramuscular vaccination, in terms of neutralizing antibodies and in preventing SARS-CoV-2 infection in both the upper and lower respiratory tracts (*Bricker et al. 2020*).

(iii) Rhesus macaques: Single-dose intranasal immunization of ChAd-SARS-CoV-2-S, in Rhesus macaques induces neutralizing antibodies and T cell responses against SARS-CoV-2. ChAd-SARS-CoV-2-S vaccine protected Rhesus monkeys against SARS-CoV-2 infection (Hassan et a*l. 2021*).

Protection against SARS-CoV-2 Variants: Further, assessment of durability, dose response, and cross-protective activity of ChAd-SARS-CoV-2-S against SARS-CoV-2 variants following

single intranasal dose induced durable high neutralizing antibodies along with S-specific IgG and IgA secreting long-lived plasma cells in the bone marrow. Protection against a historical SARS-CoV-2 strain was observed across a 100-fold vaccine dose range and over a 200-day period. At 6 weeks or 9 months after vaccination, serum antibodies neutralized SARS-CoV-2 strains, B.1.351, B.1.1.28, and B.1.617.1 spike protein and conferred almost complete protection in the upper and lower respiratory tracts after challenge with variant viruses. Thus, in mice, intranasal immunization with ChAd-SARS-CoV-2-S provides durable protection against historical and emerging SARS-CoV-2 strains (Hassan *et al. 2021b*).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tris (pH 7.4), Sodium Chloride, Magnesium Chloride, Glycerol and Polysorbate- 80

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 ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant) 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. Once opened, Multi dose vial should be used as soon as practically possible and within 6 hours when kept between +2 to +8°C.
iNCOVACC® should be discarded at the end of the immunization session or within 6 hours whichever comes first

6.4 Special precautions for storage

Store at +2° to +8 °C, do not freeze. Discard if frozen.
Shake gently before use.
Keep out of reach of children.
Protect from light.
Store vials in the original carton till the vial is used.

7. PRESENTATION

ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant) is presented in USP type 1-glass vials and PFS.
Single dose– 0.5 mL in PFS
Multi dose vial - 1mL (2 dose)

8. INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

iNCOVACC® contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant (e.g. Hydrogen peroxide-based disinfectants).

Revision date: 01 September 2022
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Marketing Authorisation Number (s):
Date of first Authorization / Renewal of Authorization:
Category for Distribution:
Vaccine (Prescription only Medicine)