



SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Confidential

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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 5×10^{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 5×10^{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.

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

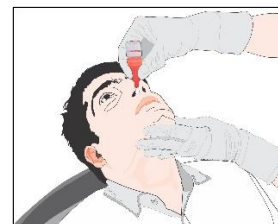
4.2 Posology and method of administration.

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

iNOVACC® 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 iNOVACC® 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 iNOVACC® 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 8°C between administrations. Post 6 hours after opening, the vials should be discarded.

iNOVACC® 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 iNOVACC® should be postponed in individuals suffering from an acute severe febrile illness/acute infection.
- Thrombocytopenia and coagulation disorders: iNOVACC® 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		Total Solicited Adverse event reported 6
	Male	Female	
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 MNT₅₀ 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 PRNT₅₀ 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
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Phase 3 clinical trial

In Phase 3 study, the GMTs of PRNT₅₀ 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 al. 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.

iNOVACC® 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

ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant)



iNOVACC® 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

Marketing Authorisation Holder:

Name of the Company: Bharat Biotech International Ltd.

Address of the Site & Corporate Office:

Sy. No. 230, 231 and 235, Genome Valley,

Turkapally, Shamirpet Mandal,

Medchal-Malkajgiri District

Telangana State, India-500078

E-mail: feedback@bharatbiotech.com

Phone No.: +91-40-2348 0567

Fax No.: +91-40-2348 0560

Website: www.bharatbiotech.com

Marketing Authorisation Number (s):

Date of first Authorization / Renewal of Authorization:

Category for Distribution:

Vaccine (Prescription only Medicine)

FACT SHEET FOR VACCINE RECIPIENTS & CAREGIVERS



SARS-CoV-2 VACCINE BY BHARAT BIOTECH

Bharat Biotech's COVID-19 Vaccine (iNOVACC®) is administered to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. This Fact Sheet contains information to help you understand the risks and benefits of iNOVACC®.

REPORTING OF SIDE EFFECTS

As with any new medicine, this vaccine will be closely monitored to allow quick identification of any new safety information. You can help by reporting any side effects you may get after vaccination to Bharat Biotech, who is the manufacturer of iNOVACC® vaccine on 24x7 Toll-Free Number: 18001022245 or at email at pvg@bharatbiotech.com. For more information, please read this Fact Sheet carefully.

Please read this Fact Sheet for information about iNOVACC®. Talk to Vaccinator/ Officer supervising your vaccination, if you have any questions. It is your choice to receive iNOVACC®. iNOVACC® is administered with a total of 8 drops (0.5 mL per dose), 4 drops into each nostril as a 2-dose series, 4 weeks apart.

WHAT IS COVID-19?

COVID-19 disease is caused by a Coronavirus called SARS-CoV-2. This type of Coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 may experience wide range of symptoms from mild to severe category. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; loss of taste or smell of recent onset; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

WHAT IS iNOVACC®?

iNOVACC® is a nasal vaccine indicated for active immunization against SARS-CoV-2 virus infection.

WHAT SHOULD YOU MENTION TO YOUR VACCINATION PROVIDER BEFORE YOU GET iNOVACC®?

Tell the Vaccinator/ Officer supervising your vaccination about all of your medical conditions, including if you:

- Are on regular medication for any illness, for how long and for which condition.
- Have any allergies
- Have fever
- Have a coagulation/bleeding disorder or are on a blood thinner
- Are immunocompromised or are on a medicine that affects your immune system
- Are pregnant
- Have received another COVID-19 vaccine

WHO SHOULD GET iNOVACC®?

It has been approved for active immunization against SARS-CoV-2 virus infection for age ≥18 years.

WHO SHOULD NOT GET iNOVACC®?

You should not get iNOVACC® if you:

- Had a severe allergic reaction to any ingredients of the vaccine.
- Had a severe allergic reaction after a previous dose of this vaccine.
- Currently have an acute infection or fever.

WHAT ARE THE INGREDIENTS IN THE iNOVACC®?

Each 0.5 ml contains: NLT 5x10¹⁰ particles per mL of ChAd36-SARS-CoV-2 COVID-19 virus (recombinant) including excipients such as Tris (pH 7.4), Sodium Chloride, Magnesium Chloride, Glycerol, Polysorbate- 80

HOW IS iNOVACC® ADMINISTERED?

iNOVACC® is administered through the nose, as a 2-dose series, 4 weeks apart. A total of 8 drops (0.5 mL per dose), 4 drops are administered into each nostril.

HAS iNOVACC® BEEN LICENSED ?

The CDSCO India has granted permission for the sale or distribution of iNOVACC® for immunization against SARS-CoV-2 virus infection for age group ≥18 years, as per Restricted Use in Emergency Situation.

WHAT ARE THE BENEFITS OF iNOVACC®?

Phase 3 clinical trial done in 3000 participants, iNOVACC® has been shown to generate good immunity following 2 doses given 4 weeks apart. It is important to appreciate that receiving the vaccine does not mean that other precautions related to COVID-19 need not be followed.

WHAT ARE THE SIDE EFFECTS OF COVID-19 VACCINE iNOVACC®?

Side effects that have been reported include:

- Headache
- Fever
- Running nose
- Sneezing

A severe allergic reaction may very rarely occur after getting a dose of iNOVACC®, however no such event was reported in the clinical trial with iNOVACC®.

WHAT SHOULD I DO ABOUT SIDE EFFECTS?

If you experience any side effect(s), please contact/visit your health provider/ Vaccinator / Officer supervising your vaccination or immediately go to the nearest hospital. In addition, you can report side effects after vaccination to Bharat Biotech International Limited, who is the manufacturer of iNOVACC® on 24x7 Toll-Free Number: +1 800 102 2245 or email at pvg@bharatbiotech.com.

WHAT IF I DECIDE NOT TO GET iNOVACC®?

It is your choice to receive or not receive iNOVACC®.

CAN I RECEIVE iNOVACC® WITH OTHER VACCINES?

There is no scientific information yet available on the appropriateness of use of iNOVACC® along with other vaccines.

WHAT IF I AM PREGNANT?

No data exists with use of iNOVACC® Vaccine in pregnant women.

WHAT IF I HAVE ALLERGIES?

Individuals who have a known severe allergy to any component of iNOVACC® are NOT advised to be vaccinated. Each 0.5 ml of iNOVACC® contains NLT 5x10¹⁰ particles per mL of ChAd36-SARS-CoV-2 COVID-19 virus (recombinant) including excipients such as Tris (pH 7.4), Sodium Chloride, Magnesium Chloride, Glycerol, Polysorbate- 80

Individuals with a history of severe allergic reactions NOT related to vaccines or injectable medications such as environmental allergies, allergies to food, pet dander, venom, or latex- may still get vaccinated. Individuals with a history of allergies to oral medications or a family history of allergic reactions, or who might have a mild allergy to vaccines (but no anaphylaxis) may still get vaccinated.

WHAT IF I AM IMMUNOCOMPROMISED?

Individuals with HIV infection or other immunocompromised conditions, or who take immunosuppressive medications or therapies might be at increased risk for severe COVID-19. However, data is NOT currently available to establish vaccine safety and efficacy in these groups. Individuals with immunosuppression may not generate a full immune response to COVID-19.

Transplant recipients should be counselled that the vaccine's effectiveness and safety profile for them is not currently known. Transplant recipients may have a weakened immune response compared to the general population. Thus, they should be advised regarding the importance of maintaining all current guidance to protect themselves even after vaccination. Immunocompromised individuals may receive COVID-19 vaccination if they have no contraindications to vaccination.

WILL iNOVACC® GIVE ME COVID-19?

No, there is no chance of getting COVID-19 post immunization with iNOVACC®.



Manufactured and Marketed by:

Bharat Biotech International Limited Genome Valley, Turkapally, Shamirpet Hyderabad, Telangana. 500078

For use only of a Registered Medical Practitioner or Hospital or Laboratory

ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant)
iNCOVACC®

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT:

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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For excipients see section 6.1.

3. PHARMACEUTICAL FORM:

Vaccine (Liquid)

4. CLINICAL PARTICULARS**4.1 Therapeutic indication**

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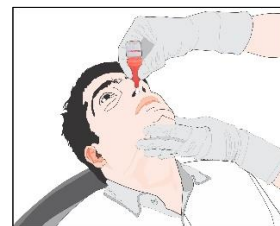
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Method of administration:

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 iNOVACC® 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 iNOVACC® 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 8°C between administrations. Post 6 hours after opening, the vials should be discarded.

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

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4.4 Special warnings and precautions for use

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- 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 iNOVACC® should be postponed in individuals suffering from an acute severe febrile illness/acute infection.
- Thrombocytopenia and coagulation disorders: iNOVACC® 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.

- **Pediatric population:** Data are not available for the use of iNOVACC® 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 for the effect of iNOVACC® on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trial Experience

Safety of the iNOVACC® 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		Total Solicited Adverse event reported 6
	Male	Female	
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%)

iNOVACC® 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 iNOVACC® with COVAXIN®, and to assess Lot to Lot Consistency of iNOVACC® 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 MNT₅₀ 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
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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 PRNT₅₀ 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 95 % CI	3.7 (1.01,13.73)	47.1 12.34,179.58

Phase 3 clinical trial

In Phase 3 study, the GMTs of PRNT₅₀ 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, Wistar rats, Syrian Hamsters and New Zealand Rabbits) was conducted based on the New Drugs and Clinical Trials 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 skin 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 al. 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

ChAd36-SARS-CoV-S COVID-19 Vaccine (recombinant)

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

Manufactured and Marketed by:



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