APPROVED FOR RESTRICTED USE IN EMERGENCY SITUATION OF COVID-19

Summary of product characteristics as per Annexure C

ANNEXURE C to MODULE I

SUMMARY OF PRODUCT CHARACTERISTICS

Doc. No. SPC/71108 Ver.1

1. NAME OF THE MEDICINAL PRODUCT.

- Novel Corona Virus 2019-nCoV Vaccine (Recombinant)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1. Novel Corona Virus 2019-nCoV Vaccine – 0.5 ml presentation (1mg/0.1ml):

Each dose consists of two shots of 0.1 ml each (2 mg per dose)

Sr. No	Material Name	Spec	Target concentration	Qty/batch	Used as
Active raw material					
1.	DNA plasmid construct with spike protein gene region from SARS-CoV-2 virus.	I.H.	1.0 mg/0.1 mL	7000 mL/batch	Antigen
Inactive raw material					
2.	Phosphate Buffered saline	I.H	--	q.s.	Buffer

2. Novel Corona Virus 2019-nCoV Vaccine – 2 ml presentation (1mg/0.1ml):

Each dose consists of two shots of 0.1 ml each (2 mg per dose)

Sr. No	Material Name	Spec	Target concentration	Qty/batch	Used as
Active raw material					
1.	DNA plasmid construct with spike protein gene region from SARS-CoV-2 virus.	I.H.	1.0 mg/0.1 mL	2500 mL/batch	Antigen
Inactive raw material					
2.	Phosphate Buffered saline	I.H	--	q.s.	Buffer

3. PHARMACEUTICAL FORM

Drug Substance(s)

- Presently, there are no approved DNA vaccines for use in humans and there is no monograph available. Novel Corona Virus 2019-nCoV Vaccine Drug Substance is developed as per In House specifications.

Drug Product

- Presently, there are no approved DNA vaccines for use in humans and there is no monograph available. Novel Corona Virus 2019-nCoV Vaccine Drug Product is developed as per In House specifications.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYCOV-D® is indicated for active immunization of individuals ≥12 years old for the prevention of coronavirus disease 2019. **ZYCOV-D®** is approved for restricted use in emergency situation of COVID-19.

4.2 Posology and method of administration

ZYCOV-D® vaccination schedule consists of 3 separate doses to be given at an interval of 28 days each (day 0, day 28 and day 56). Each dose consists of two shots of 0.1ml each given by needle free injector (Pharmajet Tropis device) via intradermal route at two separate sites (preferably deltoid region of both the arms).

Method of Administration:

ZYCOV-D® has to be given by intradermal route only using needle free injector (Pharmajet Tropis device).
Kindly refer Medication Guide for step by step guidance on Method of Administration.

4.3 Contraindications

ZYCOV-D® is contraindicated in individuals known to have hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Hypersensitivity

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Concurrent Illness

As with other vaccines, administration of ZYCOV-D® should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

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.

Duration and level of protection

The duration of protection has not yet been established. As with any vaccine, vaccination with ZYCOV-D® may not protect all vaccine recipients.

Interchangeability

No data are available on the use of ZYCOV-D® in persons that have previously received partial / complete vaccine series with another COVID-19 vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Concomitant administration of ZYCOV-D® with other vaccines has not been studied.

4.6 Special Population

Elderly Population:

Efficacy and safety data are currently limited in individuals ≥ 60 years of age. No dosage adjustment is required in elderly individuals ≥ 60 years of age.

Paediatric Population:

Efficacy and safety data are currently limited in adolescents aged 12 to <18 years. The safety and efficacy of ZYCOV-D® in children (aged <12 years old) has not yet been established.

Fertility

There is no clinical data on the effect of ZYCOV-D® on fertility.

Pregnancy

The safety and efficacy of ZYCOV-D® in pregnancy has not been established.

Breastfeeding

The safety and efficacy of ZYCOV-D® in lactating females has not been established.

4.7 Effects on ability to drive and use machines

ZYCOV-D® has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Phase I/II Study:

A total of 1048 subjects were enrolled in the Phase I/II study, comprising of 4 different arms as follows:

- Arm 1: 1mg dose given by needle and syringe
- Arm 2: 1mg dose given by Pharmajet
- Arm 3: 2mg dose given by needle and syringe
- Arm 4: 2mg dose given by Pharmajet

The age group and demographic characteristics of the subjects enrolled in Phase I/II study are as follows

Phase I: 48 adult subjects				
	Arm 1, 1 mg (0.1 mL needle and syringe)	Arm 2, 1 mg (0.1 mL Pharmajet)	Arm 3, 2 mg (0.2 mL needle and syringe)	Arm 4, 2 mg (0.2 mL Pharmajet)
Adult subjects (Male)	12	12	12	12
Mean Age (Years)	35.4	31.8	35.1	37.2
Phase II: 1000 subjects				
	Arm 1, 1 mg (0.1 mL needle and syringe)	Arm 2, 1 mg (0.1 mL Pharmajet)	Arm 3, 2 mg (0.2 mL needle and syringe)	Arm 4, 2 mg (0.2 mL Pharmajet)
N	251	249	250	250
Male	188	186	179	177
Female	63	63	71	73
Adolescent	04	06	06	02
Mean Age (Years)	35.0 ± 11.83	34.2 ± 12.11	35.4 ± 10.46	34.6 ± 10.43

Adverse events reported in Phase I Study with 2mg Pharmajet Arm:

Solicited adverse events: Tenderness at the site of injection.

Unsolicited adverse events: Low WBC count.

Adverse events reported in Phase II Study with 2mg Pharmajet Arm:

Solicited adverse events: Nausea, fatigue, injection site erythema, injection site pain, injection site pruritus, injection site swelling, pyrexia, myalgia and headache.

Frequency and Percentages of Participants with Solicited Local and systemic adverse events and unsolicited adverse events after each dose – Safety population

	ZyCoV-D n(%)			Placebo n(%)		
AE Terms	**Dose I (N = 200) n(%)**	**Dose II (N = 197) n(%)**	**Dose III (N = 194) n(%)**	**Dose I (N = 50) n(%)**	**Dose II (N = 49) n(%)**	**Dose III (N = 48) n(%)**
Solicited Local AEs						
Pain at injection site	7 (3.50)	9 (4.57)	6 (3.09)	0 (0.00)	0 (0.00)	0 (0.00)
Redness at injection site	9 (4.50)	10 (5.08)	9 (4.64)	0 (0.00)	0 (0.00)	0 (0.00)
Swelling at injection site	5 (2.50)	6 (3.05)	5 (2.58)	0 (0.00)	0 (0.00)	0 (0.00)
Itching at injection site	1 (0.50)	7 (3.55)	2 (1.03)	0 (0.00)	0 (0.00)	0 (0.00)
Muscle pain	1 (0.50)	0 (0.00)	1 (0.52)	0 (0.00)	0 (0.00)	0 (0.00)
Solicited Systemic AEs						
Fatigue	3 (1.50)	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.08)
Fever	2 (1.00)	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Headache	3 (1.50)	1 (0.51)	0 (0.00)	1 (2.00)	0 (0.00)	1 (2.08)
Nausea	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.08)
Un Solicited Systemic AEs						
Covid-19	2 (1.00)	0 (0.00)	2 (1.03)	0 (0.00)	0 (0.00)	1 (2.08)
Nasal Dryness	1 (0.50)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
High Blood Pressure	1 (0.50)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Arthralgia	0 (0.00)	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Body ache	0 (0.00)	3 (1.52)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Chikungunya virus infection	0 (0.00)	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Cough	0 (0.00)	2 (1.02)	1 (0.52)	0 (0.00)	0 (0.00)	0 (0.00)
Pyrexia	0 (0.00)	5 (2.54)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Headache	0 (0.00)	2 (1.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Myalgia	0 (0.00)	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Rhinorrhoea	0 (0.00)	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Asthenia	0 (0.00)	1 (0.51)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Dysuria	0 (0.00)	0 (0.00)	1 (0.52)	0 (0.00)	0 (0.00)	0 (0.00)
Fatigue	0 (0.00)	0 (0.00)	1 (0.52)	0 (0.00)	0 (0.00)	0 (0.00)
N = number of subjects in the specified treatment arm; n = Number of participants with the specified event						

Serious adverse events: 4 subjects experienced 7 serious adverse events: viral pneumonia, in-patient hospitalization [due to discharge at elbow site, pyrexia, arthralgia, joint swelling, erythema], surgical removal of orthopaedic implant, acute coronary syndrome, left ventricular failure with bronchopneumonia, and COVID-19 (02). None of these serious adverse events was related to IP.

All the adverse events reported in Phase I/II studies resolved without sequelae.

Adverse Events reported from Phase III Study - 2mg-3dose regimen (Interim data):
In our ongoing Phase III clinical trial, a total of 27703 subjects have been enrolled till the interim analysis. Amongst them more than 900 subjects belonged to the adolescent age group (12-17 years).

The age group and demographic characteristics of the subjects enrolled in Phase III study are as follows:

Phase III: 27703 subjects (Data at the time of interim analysis), Total sample size: 28216			
	Vaccine, 2 mg (0.2 mL Pharmajet)	Placebo	Total
Age (in Years) Mean	36.4	36.6	36.5
Age (12-17)	448	487	935
Age (18-60)	12364	12338	24702
Age (above 60)	1039	1027	2066
Gender			
Female	4506	4605	9111
Male	9345	9247	18592
Subjects at risk(Co-morbidities)	709	740	1449
Stable Chronic Heart Disease	167	155	322
Stable Chronic Lung Disease	13	7	20
Controlled Diabetic	275	289	564
Stable Liver Disease	2	3	5
Severe Obesity	18	14	32
Other Stable Co-morbid	295	293	588

The safety profile of the adolescent age group and the overall population has been found to be same. The common solicited and unsolicited adverse events reported in total population are as under:

Solicited Local Adverse Events: The most frequently reported solicited local adverse events across all treated subjects in both groups (ZYCOV-D® and Placebo) were pain at injection site: (0.66% and 0.62% after Dose 1; 0.34% and 0.35% after Dose 2 and 0.27% and 0.26% after Dose 3), redness: (0.31% and 0.28% after Dose 1; 0.19% and 0.09% after Dose 2 and 0.17% and 0.09% after Dose 3), swelling: (0.27% and 0.28% after Dose 1; 0.08% and 0.06% after Dose 2 and 0.09% and 0.05% after Dose 3) and itching: 0.08% and 0.14% after Dose 1; 0.05% and 0.07% after Dose 2 and 0.02% and 0.05% after Dose 3). Most of the adverse events were mild or moderate in severity. These events were comparable between ZYCOV-D® and placebo groups.

Solicited Systemic Adverse Events: The most commonly reported solicited systemic adverse events across all treated subjects in both groups (ZYCOV-D® and Placebo) were headache (0.25% and 0.22% after Dose 1; 0.20% and 0.24% after Dose 2 and 0.16% and 0.17% after Dose 3), fever (0.20% and 0.14% after Dose 1; 0.14% and 0.21% after Dose 2 and 0.13% and 0.10% after Dose 3), muscle pain (0.19% and 0.28% after Dose 1; 0.11% and 0.18% after Dose 2 and 0.11% and 0.09% after Dose 3), and fatigue (0.19% and 0.19% after Dose 1; 0.14% and 0.16% after Dose 2 and 0.09% and 0.13% after Dose 3). Most of the adverse events were mild or moderate in severity. These events were comparable between ZYCOV-D® and placebo groups.

Unsolicited Adverse Events: Arthralgia, Back pain, Muscle spasms, Myalgia, Musculoskeletal pain, Neck pain, Vertigo, Diarrhoea, Gastritis, Gastrooesophageal reflux disease, Nausea, Vomiting, Asthenia, Chills, Eye irritation, Abdominal distension, Abdominal pain, Fatigue, Pain, Pyrexia, Nasopharyngitis, Pain in extremity, Ageusia, Anosmia, Cerebral infarction, Dizziness, Headache, Cough, Dyspnoea, Nasal dryness, Oropharyngeal pain, Rhinorrhoea, Sneezing.

Serious adverse events: As per interim analysis report, 15 serious adverse events were identified: stroke (02), Death due to Cardiorespiratory arrest with septicaemia and alcoholic liver disease (1), Death due to COVID19 (1), Gram negative enteritis (1) and COVID19 (10). None of these serious adverse events was related to IP.

4.9 Overdose

Experience of overdose is limited.

There is no specific treatment for an overdose with ZYCOV-D® In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. PHARMACOLOGICAL PROPERTIES

The plasmid construct of ZYCOV-D® carrying the spike-S gene of interest enters host cells, where it remains in the nucleus as an episome; without getting integrated into the host cell DNA. Thus, using the host cell's protein translation machinery, the inserted cloned gene in the episome will direct the synthesis of the antigen it encodes. The protein produced by plasmid-transfected cells is likely to be expressed within the cell and folded in its native conformation. Further the signal peptide prompts cells to translocate the protein, usually to the cellular membrane. The antigen is recognized by antigen presenting cells (APCs) and further induces antibodies including neutralizing antibodies and cellular immune response through major histocompatibility complex (MHC).

5.1 Pharmacodynamics properties

Immunogenicity Data 28 days after last dose from Phase II and Phase III Clinical Trials (2mg-3dose regimen with Pharmajet):

Phase II Clinical Trial:

Parameter	Data
Seroconversion rate based on IgG* (%)	91.28%
Seroconversion rate based on Neutralizing Antibody response^ (%)	88.89%
GMT based on Neutralizing Antibody response^	131.32 (63.50, 271.58)[$]
GMFR based on Neutralizing Antibody response^	22.56 (10.57, 48.16) [$]
*by S1 antigen ELISA ^Wild type virus neutralization assay ($PRNT_{50}$) [$] data presented as Geometric Mean (95% CI)	

Phase III Clinical Trial:

Parameter	Data
Seroconversion rate based on IgG* (%)	93.33%
GMT based on IgG*	952.67 (707.9, 1282.0) $
GMFR based on IgG*	136.09 (101.11, 183.1) $
*by S1 antigen ELISA $ data presented as Geometric Mean (95% CI)	

Interim Efficacy Data from Phase III Clinical Trial (2mg-3dose regimen with Pharmajet):

A total of 27703 subjects were enrolled in the Phase III study till interim analysis. The interim primary efficacy analysis was based on the Per-Protocol analysis, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2) and who had received 3 doses of investigational product. Total of 12350 subjects who had completed 84±3 days in vaccine group and total 12320 subjects who had completed 84±3 days in placebo group were considered for analysis. Out of 81 symptomatic RT-PCR positive COVID-19 cases considered for interim analysis, 61 were in placebo group and 20 were in the vaccine (ZYCOV-D®) group. On the basis of calculation, ZYCOV-D® vaccine efficacy is 66.6% (95% CI: 47.6 to 80.7).

5.2 Pharmacokinetic properties

- Not applicable

5.3 Preclinical safety data

5.3.1 Animal Pharmacology:

The immunogenicity potential of ZYCOV-D® has been evaluated in mice, guinea pig and rabbit models by intradermal route at varying dose levels. Immunogenicity studies in animals demonstrated that the candidate DNA vaccine induces robust antibody response including neutralizing antibodies against SARS-CoV-2 and also provided Th-1 response as evidenced by elevated IFN-γ levels. In animal studies primary antibody response starts mounting in serum

two weeks after two doses and reaches peak two weeks after third immunization. The serum IgG levels against spike antigen in mice were maintained even after three months post last dosing suggesting a long-term immune response generated by the DNA vaccine candidate.

Protective efficacy of ZYCOV-D® was also evaluated in Rhesus Macaques. We assessed the immunogenicity and protective efficacy of two formulations (1mg and 2mg) of ZYCOV-D® administered either through Needle Free Injection System (NFIS) and syringe needle (intradermal) with three dose vaccine regimens. ZYCOV-D® demonstrated good immunogenicity as can be seen by the analysis of SARS-CoV-2 specific IgG (S1), Neutralizing Antibody (Nab) titres, percentage lymphocytes and cytokines response during immunization and after virus challenge. The viral clearance in nasal swab (NS), throat swab (TS), and bronchoalveolar lavage (BAL) in animals receiving ZYCOV-D® was seen demonstrating protective efficacy.

5.3.2 Animal Toxicology

Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity. Animal studies evaluating potential toxicity to reproduction and development have not yet been completed.

28-day repeat dose preclinical toxicology (PCT) studies were conducted in Wistar rats and New Zealand white rabbits and the vaccine was found to be safe and well-tolerated. Indeed, no treatment related adverse effects and behavioral changes were observed in animals during the studies. Further, histopathological examination reveals no changes of toxicological significance at high dose of 3mg (1.5 times the intended single human dose) and 6mg (3 times the intended single human dose) in rats and rabbits respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not Applicable, as no excipient is being used.

6.2 Incompatibilities

This vaccine should not be mixed with any other medicinal product.

6.3 Shelf life

The expiry date of vaccine is indicated on the label and packaging. Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +8ºC. All opened multidose vials of ZYCOV-D® should be discarded at the end of immunization session or within 6 hours whichever comes first.

6.4 Special precautions for storage

Store at 2° to 8°C. Do Not Freeze. In case of unexpected freezing of vaccine at 2-8ºC storage, it can be administered after thawing.
Multidose Vials: To be used within 6 hours of opening.

6.5 Nature and contents of container

ZYCOV-D® is supplied in a USP type-1 tubular glass vial.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Details of manufacturer

Cadila Healthcare Ltd
Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47
Sarkhej- Bavla N.H. 8A, Opp. Ramdev Masala,
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Dist. Ahmedabad – 382 213
Phone: +91-2717- 664600

8. MARKETING AUTHORISATION NUMBER(S)

MF/BIO/21/000081

9. DATE OF FIRST AUTHORISATION

20-Aug-2021