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

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

COVISHIELD

1 NAME OF THE MEDICINAL PRODUCT

COVISHIELD

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

The vaccine fulfils WHO requirements for COVID-19 vaccine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) 5×10^{10} virus particles (vp)

*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

Both **COVISHIELD** (manufactured by Serum Institute of India Pvt Ltd) and COVID-19 Vaccine AstraZeneca (manufactured by AstraZeneca) are ChAdOx1 nCoV- 19 Corona Virus Vaccines (Recombinant).

3 PHARMACEUTICAL FORM

Solution for injection

The solution is colourless to slightly brown, clear to slightly opaque and particle free with a pH of 6.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COVISHIELD is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19) - (See section 4.4 and 5.1).

The use of the vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

COVISHIELD should be administered by trained healthcare professional.

Posology

COVISHIELD vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 to 12 weeks after the first dose (see section 5.1).

It is recommended that individuals who receive a first dose of **COVISHIELD** complete the vaccination course with **COVISHIELD** (see section 4.4).

Special populations

Elderly population

No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Paediatric population

The safety and efficacy of **COVISHIELD** in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

COVISHIELD is for intramuscular (IM) injection only, preferably in the deltoid muscle.

For instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine should not receive a second dose of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant).

4.4 Special warnings and special precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant).

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. Close observation for at least 15 minutes is recommended following vaccination.

A second dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to the first dose of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant).

Concurrent illness

As with other vaccines, administration of **COVISHIELD** 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.

Thromboembolism and Thrombocytopenia

A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed following vaccination with ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) during post-authorisation use. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome.

Whilst specific risk factors for thromboembolism in combination with thrombocytopenia have not been identified, cases have occurred in patients with a previous history of thrombosis, as well as in patients with autoimmune disorders, including immune thrombocytopenia. The benefits and risks of vaccination should be considered in these patients.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as a severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain or unusual skin bruising and or petechia a few days after vaccination.

Individuals diagnosed with thrombocytopenia within 21 days of vaccination with ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant), should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 21 days of vaccination should be evaluated for thrombocytopenia.

Healthcare professionals should consult applicable guidance and, if available, seek advice from specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, **COVISHIELD** 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.

Neurological events

Very rare events of demyelinating disorders have been reported following vaccination with ChAdOx1 nCoV-19 vaccine. A causal relationship has not been established.

As with other vaccines, the benefits and potential risks of vaccinating individuals with **COVISHIELD** should be considered.

Immunocompromised individuals

It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Duration and level of protection and limitation of effectiveness

The duration of protection has not yet been established.

Protection starts from approximately 3 weeks after the first dose of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). Individuals may not be fully protected until 15 days after the second dose is administered.

As with any vaccine, vaccination with **COVISHIELD** may not protect all vaccine recipients (See section 5.1).

Interchangeability

There are no safety, immunogenicity or efficacy data to support interchangeability of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) with other COVID-19 vaccines.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, and is considered to be essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

The safety, immunogenicity and efficacy of co-administration of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) with other vaccines have not been evaluated.

4.6 Fertility, pregnancy and lactation

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Pregnancy

There is a limited experience with the use of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development (See section 5.3).

Administration of **COVISHIELD** in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

It is unknown whether **COVISHIELD** is excreted in human milk.

4.7 Effects on ability to drive and use machines

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Overall summary of the safety profile from the Overseas studies:

COV001, COV002, COV003, and COV005:

The overall safety of COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] is based on an analysis of pooled data from four clinical trials (COV001, COV002, COV003, and COV005) conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 24,244 participants ≥18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,282 received at least one dose of COVID-19 Vaccine AstraZeneca with a median duration of follow-up of 4.5 months.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 89.8% were aged 18 to 64 years and 10.2% were 65 years of age or older. The majority of recipients were White (75.5%), 9.8% were Black and 3.7% were Asian; 55.8% were female and 44.2% male.

The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Following vaccination, recipients may experience multiple adverse reactions occurring at the same time (for example, myalgia/arthralgia, headache, chills, pyrexia and malaise). If a recipient reports persistent symptoms, alternative causes should be considered.

When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently. Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old).

If required, analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used to provide symptomatic relief from post-vaccination adverse reactions.

Tabulated list of adverse drug reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 - Adverse drug reactions

MedDRA SOC	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy[a]
Immune system disorders	Not known	Anaphylaxis[b]
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness[a], somnolence[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhea[a]
	Uncommon	Abdominal pain[a]
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis[a], pruritis[a], rash[a], uriticaria[a]
	Not known	Angioedema[b]
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
	Common	Pain in extremity[a]
General disorders and administration site conditions	Very common	Injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, pyrexia[c], chills
	Common	Injection site swelling, injection site erythema, influenza like illness[a,*]

[a] Unsolicited adverse reaction

[b] Identified from post-authorisation experience

[c] Pyrexia includes feverishness (very common) and fever ≥38°C (common)

* See further description of adverse reaction below

Very rare events of neuroinflammatory disorders have been reported following vaccination with COVID 19 Vaccine AstraZeneca. A causal relationship has not been established.

Summary of safety data from D8110C00001 (Phase 3 Study in US, Peru and Chile):

Additional safety of COVID-19 Vaccine AstraZeneca was established in a randomised phase III clinical trial conducted in the United States, Peru and Chile. At the time of the analysis, 32,379 participants ≥18 years old had received at least one dose, including 21,587 in the COVID-19 Vaccine AstraZeneca group and 10,792 in the placebo group.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received placebo. Overall, among the participants who received COVID-19 Vaccine AstraZeneca 77.6% were 18 to 64 years and 22.4% were ≥ 65 years of age. Seventy-nine percent of the participants were White, 8.3% were Black, 4.4% were Asian, 4.0% were American Indian or Alaska Native, 0.3% were Native Hawaiian or Other Pacific Islander, 2.4% were of multiple races and 1.7% were not reported or unknown; 44.4% were female and 55.6% male.

The safety profile observed in this Phase III study was consistent with pooled analysis of data from the United Kingdom, Brazil and South Africa (COV001, COV002, COV003, and COV005). Adverse reactions seen in this Phase III trial were observed at similar frequencies as seen in the pooled analysis except the following: feverishness (pyrexia) (0.7%), arthralgia (1.1%), injection site warmth (<0.1%) and injection site pruritus (0.2%). These adverse reactions were solicited adverse events in the COV001, COV002, COV003, and COV005 studies whereas the D8110C00001 study did not include these as solicited symptoms to report.

Post-authorisation reports of influenza-like illness

Some recipients have reported chills, shivering (in some cases rigors), and increased body temperature possibly with sweating, headache (including migraine-like headaches), nausea, myalgia and malaise, starting within a day of vaccination. These effects usually last for a day or two.

If a patient reports unusually high or prolonged fever, or other symptoms, alternative causes should be considered and appropriate advice should be provided for diagnostic investigation and medical management as required.

Summary of global post-authorisation data of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during worldwide post-authorisation use of COVID-19 Vaccine AstraZeneca.

Immune system disorders: Anaphylactic reaction (frequency: not known)

Skin and subcutaneous tissue disorders: Angioedema (frequency: not known)

Vascular disorders: A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS) in some cases accompanied by bleeding, has been observed with a frequency less than 1/100,000. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia (see section 4.4).

Blood and lymphatic system disorders: Thrombocytopenia (frequency: very rare). The majority of reported events occurred in individuals aged 18-59 years old.

Overall summary of the safety profile from the Indian study:

COVISHIELD was also safe and well tolerated in the phase 2/3 clinical trial in India. An interim analysis included data of all 1600 participants who received first dose [1200 in **COVISHIELD** group, 100 in COVID-19 Vaccine AstraZeneca group and 300 in Placebo group]. This interim analysis includes data collected until Day 57 visit (28 days after second dose) of all 1600 participants who received first dose and 1577 participants who received second dose.

Demographic characteristics were generally similar among participants across the three groups. Overall, among the participants who received **COVISHIELD**, 87.1% were aged 18 to 59 years and 12.9% were 60 years of age or older.

Overall, the incidence of solicited reactions (injection site reactions: pain, tenderness, redness, warmth, itch, swelling and induration; and systemic reactions : fever, chills, fatigue, malaise, headache, arthralgia and myalgia), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups.

Among all 1600 participants who received a first dose, a total of 19 SAEs in 19 (1·2%) participants were reported, in 15 of 1200 (1·3%, 95% CI 0·7–2·1) participants who received **COVISHIELD**, 2 (0·7%, 95% CI 0·1–2·4) who received placebo and 2 (2·0%, 95% CI 0·2–7·0) who received COVID-19 Vaccine AstraZeneca. These included COVID-19 (n=11), fracture/dislocation (n=3), malaria (n=1), megaloblastic anaemia (n=1), cataract (n=1), encephalopathy (n=1) and a vocal cord cyst (n=1). **All SAEs resolved without sequelae and none was assessed as related to study vaccine. There were no thromboembolic-associated or autoimmune-related SAEs** reported in the study.

Table 2 - Adverse drug reactions from COVISHIELD study in India (Data until Day 57 visit)

MedDRA SOC	Frequency	Adverse reactions
Gastrointestinal disorders	Common	Nausea
	Uncommon	Diarrhoea
General disorders and administration site conditions	Very common	Injection site pain
	Common	Pyrexia, malaise, fatigue, pain, chills, injection site erythema, injection site swelling, injection site induration, asthenia, injection site pruritus
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
	Uncommon	Pain in extremity, back pain, neck pain
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, somnolence
Skin and subcutaneous tissue disorders	Uncommon	Urticaria

Summary of post-authorisation data in India

The following adverse reactions were not observed during clinical trials and have been spontaneously reported during post-authorisation use of **COVISHIELD** in India.

Immune system disorders: Anaphylactic reaction (frequency: very rare), Hypersensitivity reactions (frequency: very rare).

Vascular disorders: A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS) in some cases accompanied by bleeding, has been observed with a frequency less than 1/70,000,000. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, , as well as arterial thrombosis, concomitant with thrombocytopenia (see section 4.4).

Blood and lymphatic system disorders: Thrombocytopenia (frequency: very rare).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pharmacovigilance@seruminstitute.com

4.9 Overdose

Experience of overdose is limited.

There is no specific treatment for an overdose with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, other viral vaccines, ATC code: J07BX03

Mechanism of action

COVISHIELD is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Efficacy and immunogenicity data from the Overseas studies:

Clinical efficacy

Primary analysis of pooled data from COV001, COV002, COV003, and COV005

COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] has been evaluated based on pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001 (NCT04324606), in healthy adults 18 to 55 years of age in the UK; a Phase II/III Study, COV002 (NCT04400838), in adults ≥18 years of age (including the elderly) in the UK; a Phase III Study, COV003 (ISRCTN89951424), in adults ≥18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV005 (NCT04444674), in adults aged 18 to 65 years of age in South Africa. The studies excluded participants with history of anaphylaxis or angioedema; severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with immunosuppression. In studies COV001 and COV002, licensed seasonal influenza and pneumococcal vaccinations were permitted (at least 7 days before or after their study vaccine). All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.

In the pooled analysis for efficacy, participants ≥18 years of age received two doses of COVID-19 Vaccine AstraZeneca (N=8,597) or control (meningococcal vaccine or saline) (N=8,581). Participants randomised to COVID-19 Vaccine AstraZeneca received either two standard doses [SD] (5×10^{10} vp per dose) or one low dose [LD] (2.2×10^{10} vp) followed by one SD (5×10^{10} vp), administered via IM injection. Overall, the majority of participants (83.8%) received two SD. Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 3 to 28 weeks with 77.0% of participants receiving their two doses within the interval of 4 to 12 weeks.

Baseline demographics were well balanced across COVID-19 Vaccine AstraZeneca and control treatment groups. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 91.8% of participants were 18 to 64 years old (with 8.2% aged 65 or older); 56.0% of subjects were female; 74.9% were White, 10.1% were Black and 3.7% were Asian. A total of 3,056 (35.5%) participants had at least one pre-existing comorbidity (defined as a BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes). At the time of primary analysis the median follow up time post-dose 1 and post-dose 2 was 143 days and 83 days, respectively.

Final determination of COVID-19 cases were made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of 332 participants had SARS-CoV-2 virologically confirmed (by nucleic acid amplification tests) COVID-19 occurring ≥15 days post dose 2 with at least one COVID-19 symptom [objective fever (defined as ≥37.8°C)], cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-CoV-2 infection. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2a).

Table 2a - COVID-19 Vaccine AstraZeneca efficacy against COVID-19 in COV001, COV002, COV003 and COV005[a]

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
Primary analysis population					
Overall (SDSD + LDSD)	8597	84 (0.98)	8581	248 (2.89)	66.73 (57.41, 74.01)
Licensing regimen					
SDSD	7201	74 (1.03)	7179	197 (2.74)	63.09 (51.81, 71.73)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; LD = Low Dose; SD = Standard Dose.

[a] Primary study endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses (SDSD or LDSD) and were on-study ≥15 days post second dose.

[b] Virologically confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.

The level of protection gained from one SD of COVID-19 Vaccine AstraZeneca was assessed in an exploratory analysis that included participants who had received one dose of SD. Participants were censored from the analysis at the earliest time point of when they received a second dose or at 12 weeks post-dose 1. In this population, vaccine efficacy from 22 days post-dose 1 was 71.42% (95% CI: 51.11; 84.08 [COVID-19 Vaccine AstraZeneca 18/9,335 vs control 63/9,312]).

Exploratory analyses showed that increased vaccine efficacy was observed with increasing dose interval, see Table 2b.

Table 2b - COVID-19 Vaccine AstraZeneca efficacy by dosing interval in COV001, COV002, COV003 and COV005[a]

Dosing interval	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
< 6 weeks	3,905	35 (0.90)	3,871	76 (1.96)	55.09 (33.0, 69.90)
6-8 weeks	1,124	20 (1.78)	1,023	44 (4.30)	59.72 (31.68, 76.25)
9-11 weeks	1,530	14 (0.92)	1,594	52 (3.26)	72.25 (49.95, 84.61)
≥ 12 weeks	2,038	15 (0.74)	2,093	76 (3.63)	79.99 (65.20, 88.50)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval.

[a] Primary study endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses (SDSD or LDSD) and were on-study ≥15 days post second dose.

[b] Virologically confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.

Efficacy against COVID-19 hospital admission and severe COVID-19 disease

COVID-19 Vaccine AstraZeneca reduced COVID-19 hospitalisation (WHO severity grading ≥4).

In participants who had received two doses of COVID-19 Vaccine AstraZeneca (SDSD + LDSD, ≥15 days post-dose 2) as compared to control, there were 0 (N=8,597) vs 9 (0.10%; N=8,581) cases of hospitalised COVID-19, respectively. Corresponding to a vaccine efficacy of 100% (97.5% CI: 50.19; Not Evaluable).

In all participants who received SD as a first dose, as from 22 days post-dose 1, the vaccine efficacy was 100% (97.5% CI:69.92; Not Evaluable) with 0 (N=9,335) cases of COVID-19 hospitalisation in participants who received COVID-19 Vaccine AstraZeneca, when compared to 14 (0.15%, N=9,312) cases reported for control. Two of the COVID-19 cases reported for control (≥22 days post-dose 1) were severe (WHO severity grading ≥6).

Efficacy against COVID-19 in subgroups

Participants who had one or more comorbidities had a vaccine efficacy of 62.71% [95% CI: 44.79; 74.82]; 34 (1.11%) vs 93 (3.00%) cases of COVID-19 for COVID-19 Vaccine AstraZeneca (SDSD + LDSD, ≥15 days post-dose 2, N=3,056) and control (N=3,102), respectively; which was similar to the vaccine efficacy observed in the overall population.

In participants ≥65 years old who had received 2 doses of COVID-19 Vaccine AstraZeneca (SDSD + LDSD, ≥15 days post-dose 2, N=703), there were 4 cases of COVID-19 compared to 8 cases for control (N=680), corresponding to a vaccine efficacy of 51.91% [95% CI: -59.98, 85.54]). A large proportion (89.6%) of older adults received their second dose <6 weeks after their first. In older adults (≥65 years old) who had received SD as a first dose (≥22 days post-dose 1), there were 6 cases of COVID-19 for COVID-19 Vaccine AstraZeneca (N=945) compared to 13 for control (N=896), with 0 vs 2 cases in the COVID-19 Vaccine AstraZeneca and control groups, respectively, leading to hospitalisation (WHO severity grading ≥4).

Analysis of efficacy data from D8110C00001

COVID-19 Vaccine AstraZeneca has been evaluated based on an analysis from a randomised, double-blinded, placebo-controlled Phase III trial conducted in the United States, Peru and Chile. The trial randomised 32,451 healthy adults or those with medically-stable chronic diseases ≥18 years of age. The study excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with severe immunosuppression. All participants are planned to be followed for up to 1 year for assessments of efficacy against COVID-19 disease.

In the updated primary efficacy analysis 26,212 participants received two doses of COVID-19 Vaccine AstraZeneca (N=17,662) or placebo (N=8,550). Participants randomised to COVID-19 Vaccine AstraZeneca received (5×10^{10} vp per dose) administered via IM injection on Day 1 and Day 29 (-3 to +7 days). The median dose interval was 29 days and the majority of participants received the second dose ≥26 to ≤36 days (95.7% and 95.3%, respectively) after dose 1.43.

Baseline demographics were balanced across the COVID-19 Vaccine AstraZeneca and the placebo groups. Of the participants who received COVID-19 Vaccine AstraZeneca, 79.1% were aged 18 to 64 years and 20.9% were ≥65 years of age; 43.8% of subjects were female. Of those randomized, 79.3% were White, 7.9% were Black, 4.2% were Asian, 4.2% were American Indian or Alaska Native, 0.3% were Native Hawaiian or Other Pacific Islander, and 2.4% were of multiple races (1.7% were unknown or not reported). A total of 10,376 (58.8%) participants who received COVID-19 Vaccine AstraZeneca versus 5,105 (59.7%) who received placebo had at least one pre-existing comorbidity. At the time of analysis, the median follow up time post-dose 2 was 61 days.

Comorbidity was defined as a chronic kidney disease, chronic obstructive pulmonary disease (COPD), lower immune health because of a solid organ transplant, history of obesity (BMI>30), serious heart conditions, sickle cell disease, type 1 and 2 diabetes, asthma, dementia, cerebrovascular diseases, cystic fibrosis, high blood pressure, liver disease, scarring in the lungs (pulmonary fibrosis), thalassemia, history of smoking.

Final determination of COVID-19 cases was made by an adjudication committee. A total of 203 participants had SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose and met either the Category A or Category B criteria, and had no prior evidence of a previous SARS-CoV-2 infection

Category A: One or more of the following:

- Pneumonia diagnosed by chest x-ray, or computed tomography scan
- Oxygen saturation of ≤94% on room air or requiring either new initiation or escalation in supplemental oxygen
- New or worsening dyspnoea/shortness of breath

Category B: Two or more of the following:

- Fever >100°F (>37.8°C) or feverishness
- New or worsening cough
- Myalgia/muscle pain
- Fatigue that interferes with activities of daily living
- Vomiting and/or diarrhoea (only one finding to be counted toward endpoint definition)
- Anosmia and/or ageusia (only one finding to be counted toward endpoint definition)

COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to placebo (see Table 3).

Table 3 - COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

	COVID-19 Vaccine AstraZeneca		Placebo		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
Updated Primary Efficacy Analysis[c]					
Symptomatic Illness	17,662	73 (0.4)	8,550	130 (1.5)	73.98 (65.34, 80.47)
Key Secondary Efficacy Analyses					
Symptomatic Illness Regardless of Evidence of Prior COVID-19 Infection	18,563	76 (0.4)	9,031	135 (1.5)	73.68 (65.13, 80.13)
Severe or Critical Symptomatic COVID-19[d]	17,662	0 (0.0)	8,550	8 (< 0.1)	100.0 (71.62, NE)[e]
COVID-19 Emergency Department Visits	17,662	1 (< 0.1)	8,550	9 (0.1)	94.80 (58.98, 99.34)
Post-treatment response for SARS- CoV-2 Nucleocapsid	17,662	156 (0.9)	8,550	202 (2.4)	64.32 (56.05, 71.03)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval;

[a] Based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses and were on-study ≥15 days post second dose.

[b] Virologically confirmed SARS-CoV-2 using the Category A and B criteria.

[c] Updated primary analysis included all outstanding adjudicated events.

[d] Based on laboratory-confirmed COVID-19, plus any of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥ 125 beats per minute, oxygen saturation ≤ 93% on room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio < 300 mmHg); or respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation), evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurological dysfunction; or admission to an intensive care unit, or death.

[e] 97.5%CI

[f] Negative at baseline to positive post treatment with study intervention.

In the pre-specified primary efficacy analysis, based on 190 adjudicated cases, there were 65 (0.4%) COVID-19 cases in participants receiving COVID-19 Vaccine AstraZeneca (N=17,817) and 125 (1.5%) COVID-19 cases in participants receiving placebo (N=8,589), with a vaccine efficacy of 76.0%, [95% CI 67.6, 82.2].

When cumulative incidence of viral shedding was examined with cases occurring ≥15 days post-dose-2, time to clearance of SARS-CoV-2 in saliva samples in COVID-19 Vaccine AstraZeneca participants was notably shorter (11 vs 16 days).

Efficacy in subgroups

Participants with one or more comorbidities who received the COVID-19 Vaccine AstraZeneca ≥15 days post-dose-2 had an efficacy of 75.24% (64.18, 82.88) and participants without comorbidities had a vaccine efficacy of 71.81% (95% CI: 55.5, 82.14).

In participants ≥ 65 years old who had received COVID-19 Vaccine AstraZeneca (≥15 days post-dose N=3,696), there were 5 (0.1%) cases of COVID-19 compared to 14 (0.8%) cases for placebo (N=1,812), corresponding to a vaccine efficacy of 83.5% [95% CI: 54.17, 94.06].

Immunogenicity

Primary analysis of pooled data from COV001, COV002, COV003, and COV005

Following vaccination with COVID-19 Vaccine AstraZeneca, in participants who were seronegative at baseline, seroconversion (as measured by a ≥ 4 fold increase from baseline in S-binding antibodies) was demonstrated in ≥ 98% of participants at 28 days after the first dose and >99% at 28 days after the second. Higher S-binding antibodies were observed with increasing dose interval (Table 4).

Generally similar trends were observed between analyses of neutralising antibodies and S-binding antibodies. An immunological correlate of protection has not been established; therefore, the level of immune response that provides protection against COVID-19 is unknown.

Table 4 - SARS CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca[a,b]

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
Overall	(N=1538) 57.1 (53.8, 60.6)	(N=1466) 8358.0 (7879.2, 8866.0)	(N=1511) 30,599.8 (29,137.1, 32,135.9)
Dose Interval			
< 6 weeks	(N=578) 61.4 (55.3, 68.0)	(N=578) 8,184.5 (7,423.9, 9,023.1)	(N=564) 21,384.2 (19,750.7, 23,152.8)
6-8 weeks	(N=339) 56.1 (49.6, 63.3)	(N=290) 9,103.9 (8,063.1, 10,279.1)	(N=331) 28,764.8 (25,990.8, 31,834.9)
9-11 weeks	(N=331) 53.6 (47.5, 60.4)	(N=309) 8,120.9 (7,100.2, 9,288.4)	(N=327) 37,596.1 (34,494.2, 40,976.8)
≥ 12 weeks	(N=290) 54.3 (47.6, 61.9)	(N=289) 8,249.7 (7,254.5, 9,381.4)	(N=289) 52,360.9 (47,135.2, 58,165.9)

N = Number of subjects included in each group; GMT = Geometric mean titre; CI = Confidence interval; S = Spike

[a] Immune response evaluated using a multiplex immunoassay. [b] Individuals were seronegative at baseline.

The immune response observed in participants with one or more comorbidities was consistent with the overall population.

High seroconversion rates were observed in older adults (≥65 years) after the first SD (97.3% [N=149, 95% CI: 93.3; 99.3]) and the second SD (100.0% [N=156, 95% CI: 97.7; Not Evaluable]). The majority of older adults had a dose interval of < 6 weeks. The increase in S-binding antibodies for older adults with a dose interval of < 6 weeks (28 days after second SD: GMT=18759.6 [N=126, 95% CI: 15,764.8; 22,323.3]) was comparable to all participants who received their second dose after an interval of < 6 weeks (Table 3). The majority of participants ≥ 65 years old had a dose interval of < 6 weeks, which may have contributed to the numerically lower titres observed.

In participants with serological evidence of prior SARS-CoV-2 infection at baseline (GMT=10,979.1 [N=36; 95% CI: 6,452.7; 18,680.5]), S-antibody titres peaked 28 days after dose 1 (GMT=139,010.4 [N=35; 95% CI: 95,429.0; 202,495.1), but did not increase further after the second dose.

Spike-specific T cell responses as measured by IFN-γ enzyme-linked immunospot (ELISpot) assay are induced after a first dose of COVID-19 Vaccine AstraZeneca. Geometric mean responses are generally similar across age strata and regardless of presence of comorbidity. These do not rise further after a second dose. Th1 cytokines are induced by COVID-19 AstraZeneca with cells expressing IFN-γ, IL-2, and/or TNFα which are generally similar between age categories.

Immunogenicity data from the Indian study:

GMTs of IgG antibodies against spike (S) protein were comparable between the groups at baseline – Day 1. GMTs increased significantly after each dose of vaccine in both the groups and were comparable. There was > 98% seroconversion in both the groups on Day 57. The immunogenicity data indicates that **COVISHIELD** is comparable in terms of anti-S IgG antibody titers and seroconversion rates to COVID-19 Vaccine AstraZeneca vaccine (see Tables 5 and 6).

Table 5 Summary of Anti-S IgG antibodies

Timepoint	Statistic	COVISHIELD (N=297) n (%)	COVID-19 Vaccine AstraZeneca (N=98) n (%)
Baseline	N GMT 95% CI	297 95.4 (78.1, 116.6)	98 79.4 (58.2, 108.4)
28 days after Dose 1	N GMT 95% CI	296 10045.4 (8473.2, 11909.2)	98 6660.8 (4836.3, 9173.7)
28 days after Dose 2	n GMT 95% CI	293 30245.6 (26794.0, 34141.8)	95 28558.3 (23479.3, 34735.8)

Table 6 Summary of Proportion of Participants with Seroconversion for Anti-S IgG Antibodies

Timepoint	Statistic	COVISHIELD (N=297)	COVID-19 Vaccine AstraZeneca (N=98)
28 days after Dose 1	N Evaluated Seroconversion, n (%) 95% CI	296 286 (96.6) (93.9, 98.4)	98 90 (91.8) (84.5, 96.4)
28 days after Dose 2	N Evaluated Seroconversion, n (%) 95% CI	293 287 (98.0) (95.6, 99.2)	95 94 (98.9) (94.3, 100.0)

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Toxicity and local tolerance studies

In a repeat-dose toxicity study in mice, IM administration of COVID-19 Vaccine AstraZeneca was well tolerated. Non adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve consistent with the anticipated findings after IM injection of vaccines. There were no findings in the administration sites or sciatic nerves at the end of the recovery period, indicating complete recovery of the COVID-19 Vaccine AstraZeneca related inflammation.

Reproductive toxicity

Biodistribution studies conducted in mice did not show measurable distribution of COVID-19 Vaccine AstraZeneca to the gonads (testes, ovaries) following IM injection.

In a reproductive and development toxicity study, COVID-19 Vaccine AstraZeneca did not induce maternal or developmental toxicity following maternal exposure during the pre-mating, gestation or lactating periods. In this study, vaccine elicited detectable anti-SARS-CoV-2 S-glycoprotein maternal antibodies were transferred to the fetuses and pups, indicating placental and lactational transfer, respectively.

Mutagenicity and Carcinogenicity

COVISHIELD is a vaccine, as such, genotoxicity (mutagenicity) and carcinogenicity studies have not been concluded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate (EDTA)
Water for injection
(The names of inactive ingredients may vary according to geographical region)

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

6.3 Shelf-life

The expiry date of vaccine is indicated on the label and packaging.

Unopened multidose vial

9 months

Once opened, multi-dose vials should be kept at +2°C and +8°C and used during the immunization session or within six hours after opening, whichever comes first. All opened multidose vials of COVISHIELD™ should be discarded at the end of immunization session.

6.4 Special precautions for storage

Store in a refrigerator (+2°C to +8°C). Do not freeze. Keep vials in outer carton to protect from light. Discard if vaccine has been frozen.

Unopened multidose vial

Store at 2-8°C.
Do not freeze.
Keep vials in outer carton to protect from light.
Discard if vaccine has been frozen.

Opened multidose vial (After first use)

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

COVISHIELD is supplied as ready to use liquid in rubber-stoppered multidose vial and single dose vial in below listed presentations

2 dose - 1.0 ml per vial
10 dose - 5.0 ml per vial

6.6 Instructions for use, handling and disposal

Administration

COVISHIELD is a colourless to slightly brown, clear to slightly opaque solution. The vaccine should be inspected visually prior to administration and discarded if particulate matter or differences in the described appearance are observed.

Do not shake the vial.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly. Use a separate sterile needle and syringe for each individual. It is normal for liquid to remain in the vial after withdrawing the final dose. When low dead volume syringes and/or needles are used, the amount remaining in the vial may be sufficient for an additional dose. Care should be taken to ensure a full 0.5 ml dose is administered. Where a full 0.5 ml dose cannot be extracted, the remaining volume should be discarded. Do not pool excess vaccine from multiple vials.

The vaccine does not contain any preservative. Aseptic technique should be used for withdrawing the dose for administration.

Once opened, multi-dose vials should be kept at +2°C and +8°C and used during the immunization session or within six hours after opening, whichever comes first. Discard any unused vaccine.

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

Disposal

COVISHIELD 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).

DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

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DATE OF REVISION OF THE TEXT

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