The Special approval for the COVID-19 Vaccine by AstraZeneca during public health emergency or pandemic situation by the Brunei Darussalam Medicines Control Authority (BDMCA) is for use and supply as directed by the Government of Brunei Darussalam.

COVID-19 Vaccine AstraZeneca

COVID-19 Vaccine (ChAdOx1-S [recombinant])

Solution for Injection (IM)

1 NAME OF THE MEDICINAL PRODUCT

COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca] solution for injection in multidose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

COVID-19 Vaccine (ChAdOx1-S[*] recombinant) 5×10^{10} viral 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.
[**]Corresponding to not less than 2.5×10^8 infectious units (Inf.U)

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Clear to slightly opaque, colourless to slightly brown, particle free, pH 6.6, solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COVID-19 Vaccine AstraZeneca is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19).

4.2 Posology and method of administration

Posology

The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose (see Pharmacodynamic properties, section 5.1)

It is recommended that individuals who receive a first dose of COVID-19 Vaccine AstraZeneca complete the vaccination course with COVID-19 Vaccine AstraZeneca (see Special warnings and precautions for use, 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 COVID-19 Vaccine AstraZeneca in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

COVID-19 Vaccine AstraZeneca is for intramuscular (IM) injection only, preferably in the deltoid muscle.

For instructions on administration, see Instructions for use, handling and disposal, section 6.6..

4.3 Contraindications

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

Patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine.

4.4 Special warnings and special precautions for use

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of COVID-19 Vaccine AstraZeneca.

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

A second dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to the first dose of COVID-19 Vaccine AstraZeneca.

Concurrent illness

As with other vaccines, administration of COVID-19 Vaccine AstraZeneca 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, in some cases accompanied by bleeding, has been observed following vaccination with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca] 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 14 days following vaccination and some events had a fatal outcome.

In individuals with risk factors for thromboembolism and/or thrombocytopenia the benefits and potential risks of vaccination should be considered.

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.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca] 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 COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca]. A causal relationship has not been established.

As with other vaccines, the benefits and potential risks of vaccinating individuals with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca] 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.

Duration and level of protection

The duration of protection has not yet been established.

As with any vaccine, vaccination with COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca]may not protect all vaccine recipients.

Interchangeability

There are no safety, immunogenicity or efficacy data to support interchangeability of COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca] with other COVID-19 vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

The safety, immunogenicity and efficacy of co-administration COVID-19 Vaccine (ChAdOx1-S [recombinant]) [COVID-19 Vaccine AstraZeneca]with other vaccines have not been evaluated.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of COVID-19 Vaccine AstraZeneca in pregnant women, or women who became pregnant after receiving the vaccine. The data are insufficient to inform on vaccine-associated risk.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see Preclinical safety data, section 5.3).

As a precautionary measure, vaccination with COVID-19 Vaccine AstraZeneca is not recommended during pregnancy. Use of COVID-19 Vaccine AstraZeneca in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks.

Breastfeeding

There are no or limited data from the use of COVID-19 Vaccine AstraZeneca in lactating women. A risk to breastfed newborns/infants cannot be excluded.

In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed (see Preclinical safety data, section 5.3).

As a precautionary measure, it is preferable to avoid vaccination with COVID-19 Vaccine AstraZeneca when breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

COVID-19 Vaccine AstraZeneca has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under Undesirable effects section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Overall summary of the safety profile

The overall safety of COVID-19 Vaccine AstraZeneca is based on an analysis of pooled data from four clinical trials 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).

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

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[a]

MedDRA SOC	**Adverse reaction[b]**	**COVID-19 Vaccine AstraZeneca (N= 10,317)**	**Control[c] (N= 10,141)**
Blood and lymphatic system disorders	Lymphadenopathy[d]	Uncommon (0.3%)	Uncommon (0.3%)
Nervous system disorders	Headache	Very common (52.7%)	Very common (39.8%)
	Dizziness[d]	Uncommon (0.7%)	Uncommon (0.7%)
	Somnolence[d]	Uncommon (0.5%)	Uncommon (0.3%)
Gastrointestinal disorders	Nausea	Very common (22.2%)	Very common (13.4%)
	Vomiting	Common (1.8%)	Uncommon (0.9%)
	Diarrhoea[d]	Common (1.6%)	Common (1.5%)

MedDRA SOC	Adverse reaction[b]	COVID-19 Vaccine AstraZeneca (N= 10,317)	Control[c] (N= 10,141)
	Abdominal pain[d]	Uncommon (0.6%)	Uncommon (0.4%)
Skin and subcutaneous tissue disorders	Hyperhidrosis[d]	Uncommon (0.4%)	Uncommon (0.2%)
	Pruritus[d]	Uncommon (0.3%)	Uncommon (0.3%)
	Rash[d]	Uncommon (0.2%)	Uncommon (0.3%)
	Urticaria[d]	Uncommon (0.1%)	Uncommon (0.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (43.9%)	Very common (22.3%)
	Joint pain (Arthralgia)	Very common (26.6%)	Very common (13.0%)
	Pain in extremity[d]	Common (1.3%)	Uncommon (0.8%)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.8%)	Very common (40.1%)
	Injection site pain	Very common (54.3%)	Very common (37.5%)
	Injection site warmth	Very common (17.9%)	Very common (15.2%)
	Injection site itch (Injection site pruritus)	Very common (13.1%)	Common (7.8%)
	Injection site swelling	Common (3.4%)	Common (1.6%)
	Injection site redness (Injection site erythema)	Common (3.1%)	Common (1.4%)
	Systemic		
	Fatigue	Very common (53.0%)	Very common (38.6%)
	Malaise	Very common (44.4%)	Very common (21.0%)
	Feverishness[e] (Pyrexia)	Very common (33.5%)	Very common (11.0%)
	Chills	Very common (32.2%)	Common (8.4%)
	Fever[e] (Pyrexia)	Common (7.6%)	Common (1.5%)
	Influenza-like illness[d]	Common (1.1%)	Uncommon (0.7%)

[a] Frequencies of ADRs are reported from the safety analysis set where participants received the recommended dose (5×10^{10} vp) as their first dose.

[b] Solicited event reporting terms, where applicable MedDRA preferred terms are given in parentheses

[c] Control was either meningococcal vaccine or saline solution

[d] Unsolicited adverse reaction

[e] Defined as: Feverishness, (subjective) a self-reported feeling of having a fever; Fever, (objective) ≥38°C/100.4°F.

Summary of post-authorisation data

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 (with a frequency less than 1/100,000), in some cases accompanied by bleeding, has been observed. 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 Special warnings and precautions for use, section 4.4).

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system through the Adverse Event Following Immunisation (AEFI) Reporting Form available from the National Adverse Drug Reaction Monitoring Centre (NADRMC) and the nearest government pharmacy facility (hospital/health centre) and include batch/Lot number if available. The completed AEFI Reporting Form should be returned to the nearest government pharmacy facility (hospital/health centre) or e-mail at nadrmc.dps@moh.gov.bn

4.9 Overdose

Experience of overdose is limited.

There is no specific treatment for an overdose with COVID-19 Vaccine AstraZeneca. 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

Mechanism of action

COVID-19 Vaccine AstraZeneca 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.

Clinical efficacy

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

COVID-19 Vaccine AstraZeneca 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 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 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. In the pooled analysis, 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 4.7 months and 2.7 months, 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 COVID-19 occurring ≥15 days post second dose 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 2).

Table 2 – COVID-19 Vaccine AstraZeneca efficacy against COVID-19[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)	8,597	84 (0.98)	8,581	248 (2.89)	66.73 (57.41, 74.01)
Licensing regimen					
SDSD	7,201	74 (1.03)	7,179	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 3.

Table 3 – COVID-19 Vaccine AstraZeneca efficacy by dosing interval[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 (32.99, 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; 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.

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).

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 (SDSD)[a]

Population	Baseline[b]	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
Overall	(N=1,538)	(N=1,466)	(N=1,511)

Population	Baseline[b]	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
	57.1 (53.8; 60.6)	8,358.0 (7,879.2; 8,866.0)	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; 9023.1)	(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=18,759.6 [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 (see Table 4).

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-ɣ 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 Vaccine AstraZeneca with cells expressing IFN-γ, IL-2, and/or TNFα which are generally similar between age categories.

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.

Mutagenicity and carcinogenicity

COVID-19 Vaccine AstraZeneca is a vaccine, as such, genotoxicity (mutagenicity) and carcinogenicity studies have not been conducted.

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 foetuses and pups, indicating placental and lactational transfer, respectively.

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

Unopened multidose vial

6 months

(Please refer to the locally approved shelf-life)

Opened multidose vial

After first opening, chemical and physical in-use stability has been demonstrated from the time of vial puncture to administration for no more than:

- 6 hours at room temperature, up to 30ºC (86°F), or
- 48 hours in a refrigerator (2 to 8ºC [36 to 46°F]).

The vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours.

6.4 Special precautions for storage

Unopened multidose vial

Store in a refrigerator (2 to 8ºC [36 to 46°F]).

Do not freeze.

Store in outer carton in order to protect from light.

Opened multidose vial

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

6.5 Nature and contents of container

Multidose vial

- 5 ml of solution in a 10-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal). Packs of 10 vials.

6.6 Instructions for use, handling and disposal

Administration

COVID-19 Vaccine AstraZeneca is a colourless to slightly brown, clear to slightly opaque solution. The vaccine should be inspected visually for particulate matter and discolouration prior to administration. Discard the vial if the solution is discoloured or visible particles are observed.

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.

Each vial contains at least the number of doses stated. 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. After first opening, use the vial within:

- 6 hours when stored at room temperature (up to 30ºC [86°F]), or
- 48 hours when stored in a refrigerator (2 to 8ºC [36 to 46°F]).

The vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours. After this time, the vial must be discarded.

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

Disposal

COVID-19 Vaccine AstraZeneca 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.

EMERGENCY USE AUTHORIZATION (EUA) HOLDER: AstraZeneca UK Limited

REGISTRATION NUMBER: Not applicable.

DATE OF FIRST AUTHORISATION: 27th May, 2021

DATE OF REVISION OF THE TEXT:

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