

REG 174 INFORMATION FOR UK HEALTHCARE PROFESSIONALS

This medicinal product has been given authorisation for temporary supply by the UK Department of Health and Social Care and the Medicines & Healthcare products Regulatory Agency. It does not have a marketing authorisation, but this temporary authorisation grants permission for the medicine to be used for active immunisation of individuals aged 18 years and older for the prevention of coronavirus disease 2019 (COVID-19).

As with any new medicine in the UK, this product will be closely monitored to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 Vaccine AstraZeneca, solution for injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

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.

This product contains genetically modified organisms (GMOs).

Excipient with known effect

Each dose (0.5 ml) contains approximately 2 mg of ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals ≥ 18 years old.

The use of COVID-19 Vaccine AstraZeneca should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 18 years of age and older

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 section 5.1).

There are no data available on the interchangeability of COVID-19 Vaccine AstraZeneca with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of COVID-19 Vaccine AstraZeneca should receive the second dose of COVID 19 Vaccine AstraZeneca to complete the vaccination course.

A third dose of COVID 19 Vaccine AstraZeneca may be administered at least 8 weeks after the second dose of COVID 19 Vaccine AstraZeneca when the potential benefits outweigh any potential risks.

Elderly population

No dosage adjustment is required. See also sections 4.4 and 5.1.

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.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

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.

Individuals who have experienced thrombosis with thrombocytopenia syndrome (TTS) following vaccination with COVID-19 Vaccine AstraZeneca (see section 4.2).

Individuals who have previously experienced episodes of capillary leak syndrome (see also section 4.4).

4.4 Special warnings and 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 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.

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.

Concurrent illness

As with other vaccines, administration of COVID-19 Vaccine AstraZeneca should be postponed in individuals suffering from an acute severe febrile illness or acute infection. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

Coagulation disorders

Thrombosis with thrombocytopenia syndrome

Thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca. This includes severe 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. Some cases had a fatal outcome. The majority of these cases occurred within the first 3 weeks following vaccination but have also been reported after this period. The reporting rates have been lower after the second dose than after the first dose. Risk factors have not been identified. Some cases had increased D-dimer levels >4000ng/ml, positive platelet factor 4 antibodies and/or laboratory evidence of platelet activation.

As a precautionary measure, administration of the COVID-19 Vaccine AstraZeneca in patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) or cerebral venous sinus thrombosis should only be considered when the benefit outweighs any potential risks.

TTS requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Cerebrovascular venous and sinus thrombosis: Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca. Some cases had a fatal outcome. The majority of these cases occurred within the first four weeks following vaccination. This information should be considered for individuals at increased risk for cerebrovascular venous and sinus thrombosis. These events may require different treatment approaches than TTS and healthcare professionals should consult applicable guidance.

Thrombocytopenia

Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving COVID-19 Vaccine AstraZeneca, typically within the first four weeks after vaccination. Very rarely, these presented with very low platelet levels (<20,000 per μL) and/or were associated with bleeding. Cases with fatal outcome have been reported. Some of these cases occurred in individuals with a history of immune thrombocytopenia. If an individual has a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Vaccinated individuals should be instructed to seek immediate medical attention if four or more days after vaccination they develop new onset or worsening severe or persistent headaches with blurred vision, which do not respond to simple painkillers, or if they develop new symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, any neurological symptoms or signs such as confusion or seizures, or if they experience spontaneous bleeding, unusual skin bruising and/or petechiae beyond the site of vaccination.

Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with COVID-19 Vaccine AstraZeneca should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, 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.

Capillary leak syndrome

Very rare cases of capillary leak syndrome (CLS) have been reported in the first days after vaccination with COVID-19 Vaccine AstraZeneca. A history of CLS was apparent in some of the cases. Fatal outcome has been reported. CLS is a rare disorder characterised by acute episodes of oedema mainly affecting the limbs, hypotension, haemoconcentration and hypoalbuminaemia. Patients with an acute episode of CLS following vaccination require prompt recognition and treatment. Intensive supportive therapy is usually warranted. Individuals with a known history of CLS should not be vaccinated with this vaccine. See also section 4.3.

Neurological events

Guillain-Barré Syndrome (GBS) has been reported very rarely following vaccination with COVID-19 Vaccine AstraZeneca. Healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine AstraZeneca may be lower in immunosuppressed individuals.

If immunocompromised individuals receive a third dose, they should still be counselled to maintain physical precautions to help prevent COVID-19.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

Protection starts from approximately 3 weeks after the first dose of COVID-19 Vaccine AstraZeneca. Individuals may not be fully protected until 15 days after the second dose is administered. As with all vaccines, vaccination with COVID-19 Vaccine AstraZeneca may not protect all vaccine recipients (see section 5.1).

Excipients

Sodium

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

Ethanol

This medicinal product contains 2 mg of alcohol (ethanol) per 0.5 ml dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of COVID-19 Vaccine AstraZeneca with other vaccines has not been studied in trials conducted by AstraZeneca (see section 5.1).

Data assessed by the MHRA that support concomitant administration of COVID-19 Vaccine AstraZeneca with influenza vaccines (but at separate injection sites) are based on the ComFluCOV study [EudraCT Number: 2021-001124-18}, which investigated concomitant administration of COVID-19 Vaccine AstraZeneca with several influenza vaccines. The data show that the antibody responses are unaffected and that the reactogenicity profile is acceptable. The MHRA has needed to rely on these data in advance of them being publicly available, including to AstraZeneca, but is satisfied as to the arrangements for their expected publication, and this section will be updated once the data are published.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited experience with the use of COVID-19 Vaccine AstraZeneca 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 COVID-19 Vaccine AstraZeneca during pregnancy should only be considered when the potential benefits outweigh any potential risks (including those described in sections 4.4 and 4.8) for the mother and fetus.

Breastfeeding

It is unknown whether COVID-19 Vaccine AstraZeneca is excreted in human milk.

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 section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

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 phase I/II, II/III and III conducted in the United Kingdom, Brazil, and South Africa, and of data from an additional phase III clinical trial conducted in the United States, Peru and Chile. At the time of analysis, a total of 56,124 participants ≥ 18 years old had been randomised and of these, 33,869 participants received at least one dose of COVID-19 Vaccine AstraZeneca and 31,217 received 2 doses.

The most frequently reported adverse reactions are injection site tenderness (68%), injection site pain (58%), headache (53%), fatigue (53%), myalgia (44%), malaise (44%), pyrexia (includes feverishness (33%) and fever $\geq 38^{\circ}\text{C}$ (8%)), chills (32%), arthralgia (27%) and nausea (22%). The majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Very rare cases of thrombosis with thrombocytopenia syndrome have been reported post-marketing within the first three weeks following vaccination (see section 4.4).

When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently. The reactogenicity observed in 80 subjects who received a booster dose (third dose) 6 – 8 months after a 2-dose primary vaccination course was consistent with the known reactogenicity profile of COVID-19 Vaccine AstraZeneca and was lower than that of the first dose.

Reactogenicity events 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.

The safety profile was consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline; the number of seropositive participants at baseline was 753 (3.1%).

Tabulated list of adverse reactions

The safety profile presented below is based on an analysis of data from five clinical trials which included participants ≥ 18 years old (pooled data from four clinical trials conducted in the United Kingdom, Brazil and South Africa, and data from one clinical trial conducted in the United States, Peru and Chile) and on data from post-authorisation experience.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); 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
	Not known	Thrombocytopenia Immune thrombocytopenia
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Nervous system disorders	Very common	Headache ^a
	Uncommon	Dizziness, somnolence, lethargy
	Rare	Facial paralysis ^b
	Very rare	Guillain-Barré syndrome
Vascular disorders	Very rare	Thrombosis with thrombocytopenia syndrome ^c
	Not known	Cerebrovascular venous and sinus thrombosis Capillary leak syndrome
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea
	Uncommon	Abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis, pruritus, rash, urticaria
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
	Common	Pain in extremity
	Uncommon	Muscle spasms
General disorders and administration site conditions	Very common	Injection site tenderness, pain, warmth, pruritus, injection site bruising ^d , fatigue, malaise, feverishness, chills
	Common	Injection site swelling, erythema, pyrexia ^e , influenza-like illness, asthenia

^a Headache includes migraine (uncommon).

^b Based on data from the clinical trial conducted in the United States, Peru and Chile. Through the safety follow-up period to 05 March 2021, facial paralysis (or palsy) was reported by five participants in the COVID-19 Vaccine AstraZeneca group. Onset was 8 and 15 days after first dose and 4, 17, and 25 days after the second dose. All events were reported to be non-serious. No cases of facial paralysis were reported in the placebo group.

^c Severe and very rare cases of thrombosis with thrombocytopenia syndrome have been reported post marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

^d Injection site bruising includes injection site haematoma (uncommon, unsolicited adverse reaction)

^e Measured fever $\geq 38^{\circ}\text{C}$ (common)

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

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 lasted 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.

Reporting of suspected adverse reactions

If you are concerned about an adverse event, it should be reported on a Yellow Card. Reporting forms and information can be found at <https://coronavirus-yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in the Google Play or Apple App Store and include the vaccine brand and batch/Lot number if available.

Alternatively, adverse events of concern in association with COVID-19 Vaccine AstraZeneca can be reported to AstraZeneca on 08000 541 028 or via www.azcovid-19.com.

Please do not report the same adverse event(s) to both systems as all reports will be shared between AstraZeneca and MHRA (in an anonymised form) and dual reporting will create unnecessary duplicates.

4.9 Overdose

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

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

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 neutralising antibody and cellular immune responses.

Clinical efficacy

Pooled analysis from studies COV001/COV002/COV003/COV005

COVID-19 Vaccine AstraZeneca has been evaluated based on an interim analysis of pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001, in healthy adults 18

to 55 years of age in the UK; a Phase II/III Study, COV002, in adults ≥ 18 years of age (including the elderly) in the UK; a Phase III Study, COV003, in adults ≥ 18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV005, in adults aged 18 to 65 years of age in South Africa. The studies excluded participants with history of anaphylaxis or angioedema; participants with 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.

Based on the pre-defined criteria for interim efficacy analysis, COV002 and COV003 exceeded the threshold of ≥ 5 virologically confirmed COVID-19 cases per study and therefore contributed to the efficacy analysis; COV001 and COV005 were excluded.

In the pooled analysis for efficacy (COV002 and COV003), participants ≥ 18 years of age and seronegative at baseline received two doses of COVID-19 Vaccine AstraZeneca (N=5,807) or control (meningococcal vaccine or saline) (N=5,829). Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 4 to 26 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, 94.1% of participants were 18 to 64 years old (with 5.9% aged 65 or older); 60.7% of subjects were female; 82.8% were White, 4.6% were Asian, and 4.4% were Black. A total of 2,070 (35.6%) participants had at least one pre-existing comorbidity (defined as a BMI ≥ 30 kg/m², cardiovascular disorder, respiratory disease or diabetes). The median follow-up time post-dose 1 and post-dose 2 was 132 days and 63 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 131 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 $\geq 37.8^\circ\text{C}$), 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.

An updated efficacy analysis included 17,178 participants from all four studies. Among the participants who received COVID-19 Vaccine AstraZeneca, 83.8% were 18 to 55 years old, 10.5% were 56 to 69 years old and 5.6% were aged 70 or older. The median follow-up time post-dose 1 and post-dose 2 was 143 days and 83 days, respectively. The results of these analyses, interim and updated efficacy analyses, are presented in Table 2.

Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (CI)
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Interim analysis (cut-off date: 04 Nov 2020)					
<i>Primary (see above)</i>	5,807		5,829		
COVID-19 cases		30 (0.5)		101 (1.7)	70.4 (54.8, 80.6) ^a
Hospitalisations ^b		0		5 (0.1)	-
Severe disease ^c		0		1 (<0.1)	-
Updated analysis (cut-off date: 07 Dec 2020)					
<i>Primary (see above)</i>	8,597		8,581		
COVID-19 cases		84 (1.0)		248 (2.9)	66.7 (57.4, 74.0) ^d
Hospitalisations ^b		0		9 (0.1)	100 (50.2, NE) ^d
Severe disease ^c		0		2 (<0.1)	-

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; NE = Not Evaluable; ^a 95.84% CI; ^b WHO severity grading ≥ 4 ; ^c WHO severity grading ≥ 6 ; ^d 95% CI.

In the interim analysis, participants who had one or more comorbidities had a vaccine efficacy (VE) of 73.4% [95% CI: 48.5; 86.3]; 11 (0.5%) vs 43 (2.0%) cases of COVID-19 for COVID-19 Vaccine AstraZeneca (N=2,070) and control (N=2,113), respectively; which was similar to the VE observed in the overall population. In the updated analysis, the VE in this subgroup of participants with one or more comorbidities was 62.7% (95% CI: 44.8; 74.8 [COVID-19 Vaccine AstraZeneca 34/3,056 vs control 93/3,102]).

The number of COVID-19 cases in participants ≥ 65 years old were too few to draw conclusions on efficacy. However, in this subpopulation, immunogenicity data are available, see below. In the interim analysis there were 2 cases of COVID-19 in 660 participants. In the updated analysis, there were 12 cases in 1,383 participants (4 for COVID-19 Vaccine AstraZeneca vs 8 for control; VE = 51.9% [95% CI: -60.0, 85.5]). The majority of participants ≥ 65 years old received their doses with an interval shorter than 6 weeks.

The level of protection gained from a single dose of COVID-19 Vaccine AstraZeneca was assessed in an exploratory analysis that included participants who had received one dose. 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, VE from 22 days post-dose 1 was 73.0% (95% CI: 48.8; 85.8 [COVID-19 Vaccine AstraZeneca 12/7,998 vs control 44/7,982]). In the updated analysis, this was 69.2% (95% CI: 48.5; 82.4 [COVID-19 Vaccine AstraZeneca 20/11,044 vs control 65/11,015]).

Exploratory analyses showed that increased immunogenicity was associated with a longer dose interval (see *Immunogenicity* Table 5). Efficacy results from subgroup analyses using the updated dataset were consistent with the immunogenicity data (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, n (%)	N	Number of COVID-19 cases, n (%)	

<6 weeks	3,905	35 (0.9)	3,871	76 (2.0)	55.1 (33.0, 69.9)
6-8 weeks	1,124	20 (1.8)	1,023	44 (4.3)	59.7 (31.7, 76.3)
9-11 weeks	1,530	14 (0.9)	1,594	52 (3.3)	72.3 (50.0, 84.6)
≥12 weeks	2,038	15 (0.7)	2,093	76 (3.6)	80.0 (65.2, 88.5)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event;
CI = Confidence Interval; ^a Data from the updated analyses (07 December 2020 data cut off).

Study D8110C00001

The clinical efficacy of COVID-19 Vaccine AstraZeneca has been evaluated based on an analysis of Study D8110C00001: a randomised, double-blinded, placebo-controlled phase III study conducted in the United States, Peru and Chile. 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, pregnant women and participants with a known history of SARS-CoV-2 infection. All participants are planned to be followed for up to 12 months, for assessments of efficacy against COVID-19 disease.

Participants ≥18 years of age received two doses (5×10^{10} viral particles per dose corresponding to not less than 2.5×10^8 infectious units) of COVID-19 Vaccine AstraZeneca (N=17,662) or saline placebo (N=8,550), 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 (95.7% and 95.3% for COVID-19 Vaccine AstraZeneca and placebo, respectively) received the second dose ≥26 to ≤36 days after dose 1.

Baseline demographics were well balanced across the COVID-19 Vaccine AstraZeneca and placebo groups. Of the participants who received COVID-19 Vaccine AstraZeneca, 79.1% were aged 18 to 64 years (with 20.9% aged 65 or older) and 43.8% of subjects were female. Of those randomised, 79.3% were White, 7.9% were Black, 4.2% were Asian, 4.2% were American Indian or Alaska Native. A total of 10,376 (58.8%) participants had at least one pre-existing comorbidity, defined as: chronic kidney disease, chronic obstructive pulmonary disease, lower immune health because of a solid organ transplant, history of obesity (BMI >30), serious heart conditions, sickle cell disease, type 1 or 2 diabetes, asthma, dementia, cerebrovascular diseases, cystic fibrosis, high blood pressure, liver disease, pulmonary fibrosis, thalassemia or history of smoking. At the time of analysis the median follow-up time post-dose 2 was 61 days.

Final determination of COVID-19 cases was made by an adjudication committee. Overall vaccine efficacy and efficacy by key age groups are presented in Table 4.

Table 4 COVID-19 Vaccine AstraZeneca efficacy against symptomatic COVID-19 illness in Study D8110C00001

	COVID-19 Vaccine AstraZeneca			Placebo			Vaccine efficacy % (95% CI) ^b
	N	Number of COVID-19 cases ^a , n (%)	Incidence rate of COVID-19 per 1,000 person-years	N	Number of COVID-19 cases ^a , n (%)	Incidence rate of COVID-19 per 1,000 person-years	
Overall (age ≥18 years old)	17,662	73 (0.4)	35.69	8,550	130 (1.5)	137.23	74.0 (65.3, 80.5)
Age 18 to 64	13,966	68 (0.5)	40.47	6,738	116 (1.7)	148.99	72.8

	COVID-19 Vaccine AstraZeneca			Placebo			Vaccine efficacy % (95% CI) ^b
	N	Number of COVID-19 cases ^a , n (%)	Incidence rate of COVID-19 per 1,000 person-years	N	Number of COVID-19 cases ^a , n (%)	Incidence rate of COVID-19 per 1,000 person-years	
years old							(63.4, 79.9)
Age ≥65 years old	3,696	5 (0.1)	13.69	1,812	14 (0.8)	82.98	83.5 (54.2, 94.1)

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

CI = Confidence Interval.

^a Symptomatic COVID-19 requiring positive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and at least 1 respiratory sign or symptom, or at least 2 other systemic signs or symptoms, as defined in the protocol.

^b The confidence intervals were not adjusted for multiplicity.

Severe or critical symptomatic COVID-19 illness was assessed as a key secondary endpoint. Among all subjects in the per protocol set, no cases of severe or critical symptomatic COVID-19 were reported in the vaccine group compared with 8 cases reported in the placebo group. There were 9 hospitalised cases, the 8 cases that were adjudicated as severe or critical symptomatic COVID-19, and one additional case in the vaccine group. The majority of the severe or critical symptomatic COVID-19 cases fulfilled only the oxygen saturation (SpO₂) criterion for severe disease (≤ 93% on room air).

In individuals with or without prior evidence of SARS-CoV-2 infection, the vaccine efficacy of COVID-19 Vaccine AstraZeneca (≥15 days post-dose 2) was 73.7% (95% CI: 63.1; 80.1); 76 (0.4%) vs 135 (1.5%) cases of COVID-19 for COVID-19 Vaccine AstraZeneca (N=18,563) and placebo (N=9,031), respectively.

Participants with one or more comorbidities who received COVID-19 Vaccine AstraZeneca had an efficacy (≥15 days post-dose 2) of 75.2% (95% CI: 64.2; 82.9) and participants without comorbidities had a vaccine efficacy of 71.8% (95% CI: 55.5, 82.1).

Immunogenicity

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 5).

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 5 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=1,538) 57.1 (53.8; 60.6)	(N=1,466) 8,358.0 (7,879.2; 8,866.0)	(N=1,511) 30,599.8 (29,137.1; 32,135.9)
<i>Dose Interval</i>			
<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)

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
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 in seronegative individuals who received two recommended doses of vaccine.

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 (97.3%; N=149) and second dose (100.0%; N=156). The increase in S-binding antibodies 28 days after second dose was lower for participants ≥65 years old (GMT=19,258.5 [N=161, 95% CI: 16,650.4; 22,275.1]) when compared to participants aged 18-64 years (GMT=32,337.1 [N=1,350, 95% CI: 30,720.8; 34,038.4]). The majority of participants ≥65 years old had a dose interval of <6 weeks, which may have contributed to the 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 were induced after a first dose of COVID-19 Vaccine AstraZeneca. These did not rise further after a second dose.

Immunogenicity data in individuals receiving a booster dose (third dose)

In a substudy of COV001, antibody responses were assessed after the second and third dose in 73 participants aged 18-55 years who had received their two doses of the primary vaccination course within an 8-16 week interval, followed by a booster dose between 28-38 weeks after the second dose. Spike IgG antibody titres after the booster dose were significantly higher than after the second dose: the geometric mean [95% CI] total IgG titre was 1926 Elisa Units [1465, 2534] at 28 days after the second dose vs 3495 EUs [2833, 4312] 28 days after the booster dose (Wilcoxon signed rank test p=0.0043).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity or reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80 (E 433)
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate
Water for injections

6.2 Incompatibilities

This vaccine must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened multidose vial
6 months

The following information is intended to guide healthcare professionals only in case of an unforeseen temporary temperature excursion. It is not a recommended storage or shipping condition.

The shelf-life of unopened vials includes the following unforeseen excursions from refrigerated storage (2°C – 8°C) for a single period of:

- 12 hours up to 30°C
- 72 hours down to -3°C

Unopened vials must always be returned to refrigerated storage (2°C to 8°C) following an unforeseen temperature excursion.

The occurrence of an unforeseen temperature excursion for unopened vials does not impact how the vials should be stored after first opening (first vial puncture).

After first use

Use as soon as practically possible and within 6 hours. The vaccine may be stored between 2°C and 25°C during the in-use period.

6.4 Special precautions for storage

Unopened multidose vial

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep vials in outer carton to protect from light.

After first use

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

6.5 Nature and contents of container

Multidose vial

10-dose vial

5 ml of solution in a 10-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap. Pack sizes of 10 multidose vials.

8-dose vial

4 ml of solution in an 8-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap. Pack sizes of 10 multidose vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions and administration

This vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose. The vaccine does not contain any preservative.

Do not use this vaccine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Unopened multidose vial should be stored in a refrigerator (2°C – 8°C). Do not freeze.

Keep the vials in outer carton in order to protect from light.

COVID-19 Vaccine AstraZeneca 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. Do not dilute the solution.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

The 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. Individuals who have received the first dose of COVID-19 Vaccine AstraZeneca should receive the second dose of the same vaccine to complete the vaccination course.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly, preferably in the deltoid muscle of the upper arm. 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. After first dose withdrawal, use the vial as soon as practically possible and within 6 hours (stored at 2°C to 25°C). Discard any unused vaccine.

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 using agents with activity against adenovirus.

7. MARKETING AUTHORISATION HOLDER

Not applicable.

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

04/01/2022