WHO SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

The vaccine fulfils WHO requirements for COVID-19 vaccine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:
COVID-19 Vaccine (ChAdOx1-S* recombinant), not less than 2.5×10^8 infectious units (Inf.U), which corresponds to 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).

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 and particle free with a pH of 6.6.

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) (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

COVID-19 Vaccine AstraZeneca should be administered by a trained healthcare professional.

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 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 section 4.4).

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 section 6.6.

4.3 Contraindications

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

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
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 anaphylaxis 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.

Thrombocytopenia and coagulation disorders
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.

Neurological events
Very rare events of demyelinating disorders have been reported following vaccination with 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 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 AstraZeneca may not protect all vaccine recipients.

Interchangeability
There are no safety, immunogenicity or efficacy data to support interchangeability of COVID-19 Vaccine AstraZeneca 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 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 reproductive toxicity studies have not been completed.

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.

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

Fertility
It is unknown whether COVID-19 Vaccine AstraZeneca may impact fertility. No data are available.

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 interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,021 received at least one dose of COVID-19 Vaccine AstraZeneca.

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, 90.3% were aged 18 to 64 years and 9.7% were 65 years of age or older. The majority of recipients were White (75.5%), 10.1% were Black and 3.5% 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. 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.

Tabulated list of adverse 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
Nervous system disorders	Very common	Headache
Gastrointestinal disorders	Very common	Nausea
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, pyrexia[a], chills
	Common	Injection site swelling, injection site erythema

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

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 via the national reporting system or www.covax.azcovid-19.com.

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

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 neutralizing antibody and cellular immune responses.

Clinical efficacy
Interim analysis of pooled data from COV001, COV002, COV003, and 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 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.

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 received two doses of COVID-19 Vaccine AstraZeneca (N=5,807) or control (meningococcal vaccine or saline) (N=5,829). 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.

Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 4 to 26 weeks. The interval between the doses was longer in the LDSD group as compared to the SDSD group (71% vs 25% of participants receiving the second dose after ≥12 weeks, for LDSD and SDSD respectively).

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, 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/m^2, cardiovascular disorder, respiratory disease or diabetes). At the time of interim analysis the median follow up time post-dose 1 and post-dose 2 was 4.7 months and 2.2 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 131 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 % (95.84% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
Primary analysis population					
Overall (SDSD + LDSD)	5807	30 (0.52)	5829	101 (1.73)	70.42 (54.84, 80.63)
Licensing regimen					
SDSD	4440	27 (0.61)	4455	71 (1.59)	62.10 (39.96, 76.08)
Exploratory analysis					
LDSD	1367	3 (0.22)	1374	30 (2.18)	90.05 (65.84, 97.10)

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.

Exploratory analyses showed that increased immunogenicity was associated with a longer dose interval (see *Immunogenicity* Table 3), and a similar trend for efficacy. A longer dose interval may explain, at least partially, the higher estimates of efficacy found in the LDSD group.

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. Any participants who received a second vaccine dose were censored from the analysis at that time point. In this population, vaccine efficacy from 22 days post dose 1 was 71.30% (95% CI: 49.02; 83.84 [COVID-19 Vaccine AstraZeneca 15/6,310 vs control 52/6,296]).

COVID-19 Vaccine AstraZeneca reduced COVID-19 hospitalisation (WHO Severity grading ≥4). There were 0 (0.0%; N=5,807) cases of COVID-19 hospitalisation in participants who received two doses of COVID-19 Vaccine AstraZeneca (SDSD + LDSD, ≥15 days post dose 2) as compared to 5 (0.09%; N=5,829) for control. In all participants who received SD as a first dose, as from 22 days post dose 1, there were 0 (0.0%, N=6,307) cases of COVID-19 hospitalisation in participants who received COVID-19 Vaccine AstraZeneca (N=6,307), as compared to 9 (0.14%, N=6,297) reported for control.

Participants who had one or more comorbidities had a vaccine efficacy of 73.43% [95% CI: 48.49; 86.29]; 11 (0.53%) vs 43 (2.02%) for COVID 19 Vaccine AstraZeneca (N=2,070) and control (N=2,113), respectively; which was similar to the vaccine efficacy observed in the overall population.

The number of COVID-19 cases in participants ≥65 years old were too few to draw conclusions on efficacy. In this subpopulation, efficacy has been inferred from immunogenicity data, see below.

Immunogenicity

Interim 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 3).

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 3 SARS CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca (SDSD)[a]

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	**GMT (95% CI)**	**GMT (95% CI)**
Overall	(N=882) 57.18 (52.8, 62.0)	(N=817) 8386.46 (7758.6, 9065.1)	(N=819) 29034.74 (27118.2, 31086.7)
Dose Interval			
<6 weeks	(N=481) 60.51 (54.1, 67.7)	(N=479) 8734.08 (7883.1, 9676.9)	(N=443) 22222.73 (20360.50, 24255.3)
6-8 weeks	(N=137) 58.02 (46.3, 72.6)	(N=99) 7295.54 (5857.4, 9086.7)	(N=116) 24363.10 (20088.5, 29547.3)
9-11 weeks	(N=110) 48.79 (39.6, 60.1)	(N=87) 7492.98 (5885.1, 9540.2)	(N=106) 34754.10 (30287.2, 39879.8)

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
≥12 weeks	(N=154) 52.98 (44.4, 63.2)	(N=152) 8618.17 (7195.4, 10322.3)	(N=154) 63181.59 (55180.1, 72343.4)

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.

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 (97.8% [N=136, 95% CI: 93.7; 99.5]) and the second SD (100.0% [N=111, 95% CI: 96.7; NE]). The increase in S-binding antibodies was numerically lower for participants ≥65 years old (28 days after second SD: GMT=20,727.02 [N=116, 95% CI: 17,646.6; 24,345.2]) when compared to participants aged 18-64 years (28 days after second SD: GMT=30,695.30 [N=703, 95% CI: 28,496.2; 33,064.1]). 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=13,137.97 [N=29; 95% CI: 7,441.8; 23,194.1]), S-antibody titres peaked 28 days after dose 1 (GMT=175,120.84 [N=28; 95% CI: 120,096.9; 255,354.8]).

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. These do not rise further after a second dose.

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.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Toxicity and local tolerance studies
Non-clinical data obtained from toxicology and local tolerance studies with investigational vaccines utilising the same ChAdOx1 adenoviral vector vaccine technology as COVID 19 Vaccine AstraZeneca, concluded that the ChAdOx1 technology was well tolerated in mice and was not associated with any adverse effects.

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

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
Water for injections

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

Opened multidose vial
Use as soon as practically possible and within 6 hours.
The vaccine should be stored between 2°C and 8°C during the in-use period.

6.4 Special precautions for storage

Unopened multidose vial
Store at 2-8°C.
Do not freeze.
Keep vials in outer carton to protect from light.

Opened multidose vial
For storage conditions after first opening of the medicinal product, see 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. 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.

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 dose withdrawal, use the vial as soon as practically possible and within 6 hours (stored at 2°C to 8°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 with an appropriate antiviral disinfectant.

7. MARKETING AUTHORISATION HOLDER / EMERGENCY USE APPROVAL HOLDER OR EQUIVALENT

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)/ EMERGENCY USE APPROVAL OR EQUIVALENT

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: 15 February 2021

10. DATE OF REVISION OF THE TEXT