

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will 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

Vaxzevria suspension for injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

These are multidose vials which contain 8 doses or 10 doses of 0.5 ml per vial (see section 6.5).

One dose (0.5 ml) contains:

Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)*, not less than 2.5×10^8 infectious units (Inf.U)

*Produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology.

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

Suspension for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 18 years of age and older

The Vaxzevria vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose (see section 5.1).

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

Paediatric population

The safety and efficacy of Vaxzevria in children and adolescents (less than 18 years of age) have not yet been established. No data are available.

Elderly population

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

Method of administration

Vaxzevria is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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 handling and disposal, 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 Vaxzevria (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 and anaphylaxis

Events of anaphylaxis have been reported. 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 Vaxzevria.

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

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection. However, the presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombosis with thrombocytopenia syndrome and coagulation disorders

Thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. 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 three weeks following vaccination and occurred mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, blurred vision, confusion or seizures after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Individuals diagnosed with thrombocytopenia within three weeks after vaccination with Vaxzevria, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia.

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.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) 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 Vaxzevria. 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 Vaxzevria. 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 Vaxzevria may be lower in immunosuppressed individuals.

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 Vaxzevria. Individuals may not be fully protected until 15 days after the second dose is administered. As with all vaccines, vaccination with Vaxzevria may not protect all vaccine recipients (see section 5.1).

Currently available clinical trial data do not allow an estimate of vaccine efficacy in subjects over 55 years of age.

Excipients

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 ml dose, that is to say 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 Vaxzevria with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of Vaxzevria in pregnant women.

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

Administration of Vaxzevria during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

It is unknown whether Vaxzevria is excreted in human milk.

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

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Vaxzevria 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 Vaxzevria 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 Vaxzevria or control. Out of these, 12,282 received at least one dose of Vaxzevria and 10,448 received two doses. The median duration of follow-up was 81 days post-dose 2, with 7,158 participants completing >2 months follow-up post-dose 2.

The most frequently reported adverse reactions were injection site tenderness (63.8%), injection site pain (54.3%), headache (52.7%), fatigue (53.0%), myalgia (43.9%), malaise (44.4%), pyrexia (includes feverishness (33.5%) and fever $\geq 38^{\circ}\text{C}$ (7.6%)), chills (32.2%), arthralgia (26.6%) and nausea (22.2%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Following vaccination with Vaxzevria, recipients may experience multiple adverse reactions occurring at the same time (for example, myalgia/arthralgia, headache, chills, pyrexia and malaise).

When compared with the first dose, adverse reactions reported after the second dose were milder and less frequent.

Reactogenicity was generally milder and reported less frequently in the population of older adults (≥ 65 years old) studied (2,274 individuals [9.4%]).

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

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). 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 $< 1/1000$); very rare ($< 1/10,000$) and not known (cannot be estimated from available data); within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness.

Table 1 Adverse drug reactions

MedDRA SOC	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Common	Thrombocytopenia ^a
	Uncommon	Lymphadenopathy
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness Somnolence Lethargy
Vascular disorders	Very rare	Thrombosis with thrombocytopenia syndrome*

MedDRA SOC	Frequency	Adverse Reactions
	Not known	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
General disorders and administration site conditions	Very common	Injection site tenderness Injection site pain Injection site warmth Injection site pruritus Injection site bruising ^b Fatigue Malaise Feverishness Chills
	Common	Injection site swelling Injection site erythema Fever ^c Influenza-like illness Asthenia

^a In clinical trials, transient mild thrombocytopenia was commonly reported (see section 4.4).

^b Injection site bruising includes injection site haematoma (uncommon)

^c Measured fever $\geq 38^{\circ}\text{C}$

*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).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

There is no specific treatment for an overdose with Vaxzevria. 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: Vaccines, other viral vaccines, ATC code: J07BX03

Mechanism of action

Vaxzevria is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralising antibody and cellular immune responses, which may contribute to protection to COVID-19.

Clinical efficacy

Analysis of pooled data from COV002 and COV003

The clinical efficacy of Vaxzevria has been evaluated based on an analysis of pooled data from two on-going randomised, blinded, controlled trials: a phase II/III study, COV002, in adults ≥ 18 years of age (including the elderly) in the UK; and a phase III study, COV003, in adults ≥ 18 years of age (including the elderly) in Brazil. 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, pregnant women and participants with a known history of SARS-CoV-2 infection. Influenza vaccines could be administered 7 days before or after any dose of Vaxzevria. 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 (5×10^{10} viral particles per dose corresponding to not less than 2.5×10^8 infectious units) of Vaxzevria (N=6,106) or control (meningococcal vaccine or saline) (N=6,090), administered via IM injection.

Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 3 to 23 weeks (21 to 159 days), with 86.1% of participants receiving their two doses within the interval of 4 to 12 weeks (28 to 84 days).

Baseline demographics were well balanced across Vaxzevria and control treatment groups. In the pooled analysis, among the participants who received Vaxzevria with a dose interval of between 4 and 12 weeks, 87.0% of participants were 18 to 64 years old (with 13.0% aged 65 or older and 2.8% aged 75 or older); 55.1% of subjects were female; 76.2% were White, 6.4% were Black and 3.4% were Asian. A total of 2,068 (39.3%) participants had at least one pre-existing comorbidity (defined as a BMI ≥ 30 kg/m², cardiovascular disorder, respiratory disease or diabetes). At the time of analysis the median follow up time post-dose 2 was 78 days.

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 218 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 $\geq 37.8^\circ\text{C}$), cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-CoV-2 infection. Vaxzevria significantly decreased the incidence of COVID-19 compared to control (see Table 2).

Table 2 Vaxzevria efficacy against COVID-19^a

Population	Vaxzevria		Control		Vaccine efficacy % (95% CI) ^b
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Licensing regimen					
4 – 12 weeks (28 to 84 days)	5,258	64 (1.2)	5,210	154 (3.0)	59.5 (45.8, 69.7)

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

^a Efficacy 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 and were on-study ≥ 15 days post second dose.

^b CI not adjusted for multiplicity.

Vaccine efficacy was 62.6% (95% CI: 50.9; 71.5) in participants receiving two recommended doses with any dose interval (ranging from 3 to 23 weeks), in a pre-specified analysis.

Regarding COVID-19 hospitalisation (WHO Severity grading ≥ 4) there were 0 (0.0%; N=5,258) cases of COVID-19 hospitalisation in participants who received two doses of Vaxzevria (≥ 15 days post dose 2) as compared to 8 (0.2%; N=5,210) for control, including one severe case (WHO Severity grading ≥ 6), reported for control. In all participants who received at least one dose, as from 22 days post dose 1, there were 0 (0.0%, N=8,032) cases of COVID-19 hospitalisation in participants who received Vaxzevria, as compared to 14 (0.2%, N=8,026), including one fatality, reported for control.

Participants who had one or more comorbidities had a vaccine efficacy of 58.3% [95% CI: 33.6; 73.9]; 25 (1.2%) vs 60 (2.9%) cases of COVID-19 for Vaxzevria (N=2,068) and control (N=2,040), respectively; which was similar to the vaccine efficacy observed in the overall population.

Evidence shows protection starts from approximately 3 weeks after first dose of vaccine and persists up to 12 weeks. A second dose should be given at a 4 to 12 week interval after the first dose (see section 4.4).

Elderly population

Among participants aged between 56 and 65 years old, 8 cases of COVID-19 were reported in those receiving Vaxzevria (≥ 15 days post dose 2) compared with 9 cases for control; 2 and 6 cases of COVID-19 were reported in participants older than 65 years of age, for Vaxzevria (≥ 15 days post dose 2) and control, respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Vaxzevria in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

In a repeat-dose toxicity study in mice, IM administration of Vaxzevria 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 Vaxzevria related inflammation.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine are not expected to have genotoxic potential.

Reproductive toxicity

In a reproductive and development toxicity study, Vaxzevria did not induce maternal or developmental toxicity following maternal exposure during the pre-mating, gestation or lactating periods. In this study, vaccine elicited detectable anti-SARS-CoV-2 S-glycoprotein maternal antibodies were transferred to the fetuses and pups, indicating placental and lactational transfer, respectively. No Vaxzevria data are available on vaccine excretion in milk.

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 medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened vial

6 months when stored in a refrigerator (2°C – 8°C)

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 – 8°C) following a temperature excursion.

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

Opened vial

Chemical and physical in-use stability have been demonstrated for 6 hours when stored at temperatures up to 30°C and for 48 hours when stored in a refrigerator (2°C – 8°C). After this time, the vial must be discarded. Do not return it to the refrigerator after storage outside the refrigerator.

Alternatively, an opened vial may be stored in a refrigerator (2°C – 8°C) for a maximum of 48 hours if it is immediately returned to the refrigerator following each puncture.

From a microbiological point of view, after first opening the vaccine should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

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

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

6.5 Nature and contents of container

Multidose vial

8-dose vial

4 ml of suspension in an 8-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal). Each vial contains 8 doses of 0.5 ml. Pack sizes of 10 multidose vials.

10-dose vial

5 ml of suspension in a 10-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal). Each vial contains 10 doses of 0.5 ml. 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.

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.

The vaccine should be inspected visually for particulate matter and discolouration prior to administration. Vaxzevria is a colourless to slightly brown, clear to slightly opaque suspension. Discard the vial if the suspension is discoloured or visible particles are observed. Do not shake. Do not dilute the suspension.

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

The Vaxzevria 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 Vaxzevria 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 new needle for administration, when possible.

It is normal for liquid to remain in the vial after withdrawing the final dose. An additional overfill is included in each vial to ensure that 8 doses (vial of 4 ml) or 10 doses (vial of 5 ml) of 0.5 ml can be delivered. Do not pool excess vaccine from multiple vials. Discard any unused vaccine.

From the time of vial opening (first needle puncture) use within 6 hours when stored at temperatures up to 30°C. After this time, the vial must be discarded. Do not return it to the refrigerator. Alternatively, an opened vial may be stored in a refrigerator (2°C – 8°C) for a maximum of 48 hours if it is immediately returned to the refrigerator following each puncture.

Disposal

Any unused vaccine or waste material should be disposed of in compliance with the local guidance for pharmaceutical waste. Potential spills should be disinfected using agents with viricidal activity against adenovirus.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1529/001 10 multidose vials (8 doses per vial)
EU/1/21/1529/002 10 multidose vials (10 doses per vial)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 January 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>