▼This vaccine is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

VAXZEVRIA® (previously COVID-19 Vaccine AstraZeneca) (ChAdOx1-S) solution for injection

1 NAME OF THE MEDICINE

ChAdOx1-S

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains $5x10^{10}$ viral particles (vp) of ChAdOx1-S [a, b, c].

[a] Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein (GP)

[b] The vaccine is manufactured using material originally sourced from a human embryo (Human Embryonic Kidney cells: HEK293)

[c] Corresponding to not less than 2.5×10^8 infectious units (Inf.U)

There are two multi-dose vial presentations:

- 8 dose: $4x10^{11}$ vp of ChAdOx1-S in 4 mL.
- 10 dose: $5x10^{11}$ vp of ChAdOx1-S in 5 mL.

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opaque, colourless to slightly brown, particle free with a pH of 6.1 – 7.1.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VAXZEVRIA has **provisional approval** for the indication:

Active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

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

The decision has been made on the basis of short term efficacy and safety data. Continued approval is dependent upon the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.

4.2 DOSE AND METHOD OF ADMINISTRATION

The VAXZEVRIA primary 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 Pharmacodynamic properties).

It is recommended that individuals who receive a first dose of VAXZEVRIA receive a second dose of VAXZEVRIA (see Section 4.4 Special warnings and precautions for use).

A third (booster) dose of 0.5 mL may be given if clinically indicated with reference to official guidance regarding the use of a heterologous third dose (e.g. mRNA vaccine).

A third (booster) dose of VAXZEVRIA should be administered at least 3 months after a second-dose of VAXZEVRIA.

Special patient populations

Use in the elderly

No dosage adjustment is required in elderly individuals ≥65 years of age (see Section 5.1 Pharmacodynamic properties).

Paediatric use

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

METHOD OF ADMINISTRATION

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

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

VAXZEVRIA 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.

Using an aseptic technique, 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), or
- 48 hours when stored in a refrigerator (2ºC to 8ºC).

The vial can be re-refrigerated, but after first opening 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.

There is limited information available in relation to the storage of the vaccine in syringes. For practical reasons, if the contents of the vial are to be used within a short period of time, drawing up the content in multiple syringes at once may be considered. Vaccine in syringes may be kept for up to 6 hours when stored at room temperature (up to 30˚C). However, ensure that the cumulative storage time at room temperature from the first vial puncture to last dose administration does not exceed 6 hours. After this time, the syringe must be discarded. For more details in relation to administration, please refer to Department of Health Guidance Documents.

The vials, needles, syringes should be disposed of in the clinical waste bin (see Section 6.6 Special precautions for disposal).

4.3 CONTRAINDICATIONS

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

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

Individuals who have previously experienced episodes of capillary leak syndrome (see also Section 4.4 Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with any vaccine, vaccination with VAXZEVRIA may not protect all vaccine recipients. Vaccination does not mitigate the need to follow other official recommendations to prevent the spread of COVID-19.

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of VAXZEVRIA.

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

An additional dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to a previous dose of VAXZEVRIA.

Anxiety-related reactions

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

Concurrent illness

As with other vaccines, administration of VAXZEVRIA 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.

Coagulation disorders

Thrombosis and thrombocytopenia

A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed following vaccination with VAXZEVRIA during post-marketing use. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of the events occurred within the first 21 days following vaccination but have also been reported after this period. Some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose. See also Section 4.3 Contraindications.

The incidence of TTS following a third dose of VAXZEVRIA has not yet been determined, including in people who have received a third dose of VAXZEVRIA following another type COVID-19 vaccine.

Whilst specific risk factors for thromboembolism in combination with thrombocytopenia have not been identified, cases have occurred in patients with a previous history of thrombosis, as well as in patients with autoimmune disorders, including immune thrombocytopenia. The benefits and risks of vaccination should be considered in these patients. Cases have also occurred in patients without other risk factors for thrombosis and thrombocytopenia. As a precautionary measure, administration of VAXZEVRIA in patients with a history of cerebral venous sinus thrombosis with thrombocytopenia or heparin induced thrombocytopenia (HIT) should only be considered when the benefit outweighs any potential risks.

Venous thromboembolic events without thrombocytopenia

Venous thromboembolic events without accompanying thrombocytopenia, including events of cerebrovascular venous and sinus thrombosis (CVST) have been reported following vaccination with VAXZEVRIA. Although a causal relationship has not been established, these events can be fatal and may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance.

Thrombocytopenia

Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving VAXZEVRIA, typically within the first four weeks after vaccination. Very rarely, these presented with very low platelet levels ($<20 \times 10^9$ per L) and/or were associated with bleeding. Cases with fatal outcome have been reported.

Some of these cases occurred in individuals with a history of ITP or thrombocytopenia. If an individual has a history of a thrombocytopenic disorder, such as ITP, 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 thrombosis 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 headache, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, spontaneous bleeding or unusual skin bruising and/or petechia a few days after vaccination.

Individuals diagnosed with thrombocytopenia within 21 days of vaccination with VAXZEVRIA, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 21 days of vaccination should be evaluated for thrombocytopenia.

Since medical management of a post-vaccine thrombosis with thrombocytopenia may be different from medical management of other thromboses, if a patient presents with thrombosis and/or thrombocytopenia after receiving a vaccine, healthcare professionals should consult applicable guidance and seek advice from a specialist haematologist to diagnose and treat this condition.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, VAXZEVRIA 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 VAXZEVRIA. A history of CLS was apparent in some of these 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 support therapy is usually warranted. Individuals with a known history of CLS should not be vaccinated with this vaccine (see Section 4.3 Contraindications).

Neurological events

Guillain-Barré Syndrome (GBS) has been reported very rarely following vaccination with VAXZEVRIA.

Transverse myelitis (TM) has been reported very rarely following vaccination with VAXZEVRIA. Healthcare professionals should be alert of TM signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.

Very rare events of demyelinating disorders, including acute disseminated encephalomyelitis, have been reported following vaccination with VAXZEVRIA. A causal relationship has not been established. Healthcare professionals should be alert of signs and symptoms of demyelinating disorders to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.

Risk of very rare events after a booster dose

The risk of very rare events (such as coagulation disorders including thrombosis with thrombocytopenia syndrome, CLS, GBS and TM) after a booster dose of VAXZEVRIA has not yet been characterised.

Immunocompromised individuals

The immunogenicity, efficacy and safety of VAXZEVRIA has not been assessed in immunocompromised individuals, including those receiving immunosuppressive therapy. The immunogenicity of vaccines may be lower in immunosuppressed patients.

Duration of protection

The duration of protection has not yet been established. Studies are ongoing.

Use in individuals with significant co-morbidities

There are currently limited data available for the efficacy and safety in individuals with significant co-morbidities. The decision to immunise an individual should be made on the basis of potential benefits over risks to that individual.

Paediatric use

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

Effects on laboratory tests

Vaccination with VAXZEVRIA leads to the development of antibodies to the SARS-CoV-2 S protein. This does not interfere with results from SARS-CoV-2 PCR testing.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The safety, immunogenicity and efficacy of co-administration of VAXZEVRIA with other vaccines have not been evaluated.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a combined fertility and developmental toxicity study, female mice were intramuscularly administered $3.71x10^{10}$ virus particles (>1000 times the clinical dose of virus particles/Kg) of VAXZEVRIA 13 days before mating and on gestation day 6. SARS COV-2 glycoprotein antibodies were present in maternal animals from prior to mating to the end of the study on gestational day 17.5 as well as in fetuses. There were no vaccine-related effects on female fertility and pregnancy rate. A biodistribution study conducted in mice did not show quantifiable distribution of virus particles to the gonads (testes, ovaries) following IM injection.

Use in pregnancy – Category B1

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

Animal studies did not indicate harmful effects with respect to reproductive toxicity. In a combined fertility and developmental toxicity study, female mice were intramuscularly administered VAXZEVRIA before the start of mating (premating day 13) and gestation day 6 or twice during gestation (gestation days 6 and 15) with 3.71×10^{10} virus particles (>1000 times the clinical dose on a virus particle/Kg basis). There were no significant vaccine-related adverse effects on embryofetal development or parturition. In this study, vaccine elicited detectable anti-SARS-CoV-2 S-glycoprotein maternal antibodies were transferred to the fetuses and pups indicating placental transfer.

Use of VAXZEVRIA in pregnant women should only be considered when the potential benefits of vaccination outweigh the potential risks for the mother and fetus.

Use in lactation

There are limited data from the use of VAXZEVRIA in lactating women. It is unknown whether VAXZEVRIA is excreted in human milk. 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. In a reproductive and development toxicity study, VAXZEVRIA did not induce maternal or developmental toxicity following two vaccine doses during gestation. In this study, vaccine elicited detectable anti-SARS-CoV-2 S-glycoprotein maternal antibodies were transferred to the fetuses and pups indicating lactational transfer.

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 Adverse effects (Undesirable effects) may temporarily affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

Primary vaccination course

Overall summary of the safety profile from the pivotal Oxford clinical trials

The overall safety of VAXZEVRIA is based on an analysis (data lock: 7 December 2020) of pooled data from four clinical trials (COV001, COV002, COV003 and COV005) conducted in the United Kingdom, Brazil, and South Africa, in which 24, 221 participants ≥18 years old were randomised and received either VAXZEVRIA or control. Out of these, 12, 257 received at least one dose of VAXZEVRIA, with a median duration of placebo-controlled blinded follow-up of 6.3 months. Participants continued to be followed for safety regardless of unblinding or receipt of unblinded vaccination, and longer follow-up of ≥12 months (median 13.0 months) is available for 10, 247 participants.

Demographic characteristics were generally similar among participants who received VAXZEVRIA and those who received control. Overall, among the participants who received VAXZEVRIA, 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 from the pivotal Oxford clinical trials

Table 1 Adverse Drug Reactions (ADR) primary analysis – pooled data set from COV001, COV002, COV003, and COV005 (safety analysis set[a])

MedDRA SOC	Adverse reaction[b]	VAXZEVRIA (N= 10, 304)	Control[c] (N= 10, 141)
Blood and lymphatic system disorders	Lymphadenopathy[d]	Uncommon (0.4%)	Uncommon (0.5%)
Metabolism and nutrition disorders	Decreased appetite	Uncommon (0.6%)	Uncommon (0.2%)
Nervous system disorders	Headache	Very common (52.6%)	Very common (40.4%)

MedDRA SOC	Adverse reaction[b]	VAXZEVRIA (N= 10, 304)	Control[c] (N= 10, 141)
	Dizziness[d]	Common (1.0%)	Uncommon (0.9%)
	Somnolence[d]	Uncommon (0.5%)	Uncommon (0.4%)
Gastrointestinal disorders	Nausea	Very common (22.2%)	Very common (13.9%)
	Diarrhoea[d]	Common (2.6%)	Common (2.3%)
	Vomiting	Common (1.7%)	Common (1.0%)
	Abdominal pain[d]	Common (1.0%)	Uncommon (0.8%)
Skin and subcutaneous tissue disorders	Hyperhidrosis[d]	Uncommon (0.5%)	Uncommon (0.2%)
	Pruritus[d]	Uncommon (0.4%)	Uncommon (0.4%)
	Rash[d]	Uncommon (0.4%)	Uncommon (0.4%)
	Urticaria[d]	Uncommon (0.1%)	Rare (≤0.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (43.8%)	Very common (23.1%)
	Joint pain (Arthralgia)	Very common (26.4%)	Very common (13.4%)
	Pain in extremity[d]	Common (1.5%)	Common (1.1%)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.6%)	Very common (40.5%)
	Injection site pain	Very common (54.9%)	Very common (38.4%)
	Injection site warmth	Very common (18.4%)	Very common (15.6%)
	Injection site itch (Injection site pruritus)	Very common (13.2%)	Common (8.1%)
	Injection site swelling	Common (3.5%)	Common (1.6%)
	Injection site redness (Injection site erythema)	Common (3.1%)	Common (1.4%)
	Systemic		
	Fatigue	Very common (53.2%)	Very common (39.1%)
	Malaise	Very common (44.3%)	Very common (21.8%)
	Feverishness[e] (Pyrexia)	Very common (33.4%)	Very common (12.1%)
	Chills	Very common (31.9%)	Common (9.2%)
	Fever[e] (Pyrexia)	Common (7.8%)	Common (1.4%)
	Influenza-like illness[d]	Common (1.1%)	Uncommon (0.8%)

[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 reactions

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

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).

Summary of the safety data from Phase III clinical trial D8110C00001

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

Demographic characteristics were generally similar among participants who received VAXZEVRIA and those who received placebo. Overall, among the participants who received VAXZEVRIA 77.6% were 18 to 64 years and 22.4% were ≥65 years of age. Seventy-nine percent (79%) of the participants were White, 8.3% were Black, 4.4% were Asian, 4.0% were American Indian or Alaska Native, 0.3% were Native Hawaiian or Other Pacific Islander, 2.4% were of multiple races and 1.7% were not reported or unknown; 44.4% were female and 55.6% male.

The safety profile observed in this Phase III clinical trial was consistent with pooled analysis of data from the United Kingdom, Brazil and South Africa (pivotal Oxford clinical trials - COV001, COV002, COV003 and COV005). Adverse reactions seen in this Phase 3 clinical trial were observed at similar frequencies as seen in the pooled analysis except the following: feverishness (pyrexia) (0.7%), arthralgia (1.1%), injection site warmth (<0.1%) and injection site pruritus (0.2%). These adverse reactions were solicited adverse events in the COV001, COV002, COV003 and COV005 studies whereas the D8110C00001 clinical trial did not include these as solicited symptoms to report.

Booster dose (third dose)

The safety profile observed in individuals who received a booster dose (third dose) was consistent with the known safety profile of VAXZEVRIA. No new safety concerns, as compared with adverse reactions reported for the primary vaccination course with Vaxzevria, have been identified in individuals receiving a booster dose of Vaxzevria.

Booster dose (third dose) following primary vaccination with Vaxzevria

In Study D7220C00001, 367 participants who had previously received a 2-dose primary vaccination course with VAXZEVRIA received a single booster dose (third dose) of VAXZEVRIA. Median time between the second dose and the booster dose was 8.6 months (263 days).

The most frequently reported adverse reactions in previously VAXZEVRIA vaccinated participants were injection site tenderness (54%), fatigue (43%), injection site pain (38%), headache (34%), myalgia (23%), and malaise (22%). The majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

Booster dose (third dose) following primary vaccination with an approved COVID-19 mRNA vaccine

In Study D7220C00001, 322 participants who had previously received a 2-dose primary vaccination course with an approved COVID-19 mRNA vaccine received a single booster dose (third dose) of VAXZEVRIA. Median time between the second dose and the booster dose was 3.9 months (119 days).

The most frequently reported adverse reactions in previously mRNA vaccinated participants were injection site tenderness (71%), fatigue (58%), headache (52%), injection site pain (50%), myalgia (47%), malaise (42%), chills (31%), and nausea (21%). The majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

In the COV001 study, the observed reactogenicity in participants who received a booster dose (third dose) following a 2 dose primary vaccination course was consistent with the known reactogenicity profile of VAXZEVRIA, and was lower after the third dose compared with after the first dose.

No new safety concerns, as compared with adverse reactions reported for the primary vaccination course with VAXZEVRIA, have been identified in individuals receiving a booster dose of VAXZEVRIA.

Post-marketing experience

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

Table 2 Post-marketing adverse reactions

Frequency	System Organ Class	Event
Uncommon (≥0.1% - <1%)	*Vascular disorders*	Paraesthesia and hypoaesthesia. Many of these events were co-reported with reactogenicity events.
	Ear and labyrinth disorders	Tinnitus
Very rare (<0.01%)	*Vascular disorders*	A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia (see Section 4.4 Special warnings and precautions for use).
	Blood & lymphatic system disorders	Thrombocytopenia
	Nervous system disorders	Guillain-Barré syndrome (GBS)
Unknown [a]	*Immune system disorders*	Anaphylactic reaction
	Skin & subcutaneous tissue disorders	Angioedema Cutaneous vasculitis
	Vascular disorders	Capillary leak syndrome (see Section 4.4 Special warnings and precautions for use). Cerebrovascular venous and sinus thrombosis without thrombocytopenia
	Blood & lymphatic system disorders	Immune thrombocytopenia
	Nervous system disorders	Transverse myelitis

[a] The frequency of these adverse reactions is 'not known' (cannot be estimated from available data as the reports come from a population of unknown size).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience of overdose is limited.

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Clinical trials

This section will be updated as evidence emerges from ongoing clinical studies.

Efficacy of two doses of VAXZEVRIA

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

The efficacy and safety of VAXZEVRIA has been evaluated based on the primary analysis (data lock: 7 December 2020) of pooled data from four pivotal on-going randomised, blinded, controlled Oxford clinical studies: 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. In studies COV001 and COV002, licensed seasonal influenza and pneumococcal vaccinations were permitted (at least 7 days before or after their study vaccine).

In the pooled primary analysis for efficacy, participants ≥18 years of age received two doses of VAXZEVRIA (N=8, 597) or control (meningococcal vaccine or saline) (N=8, 581). Participants randomised to VAXZEVRIA 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 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 VAXZEVRIA and control treatment groups. In the pooled primary analysis, among the participants who received VAXZEVRIA, 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 mild 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 was 4.7 months and post-dose 2 was 2.7 months.

The primary efficacy endpoint was symptomatic COVID-19 infection, defined as objective fever (≥37.8°C), cough, shortness of breath, anosmia, or ageusia with virologically confirmed COVID-19 occurring ≥15 days post second dose, in participants without serological evidence of previous SARS-CoV-2 infection. 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 met the primary efficacy endpoint criteria. VAXZEVRIA significantly decreased the incidence of COVID-19 compared to control (see Table 3).

Table 3 VAXZEVRIA efficacy against COVID-19 in the pivotal Oxford clinical trials (COV001, COV002, COV003 and COV005)

Population	VAXZEVRIA		Control		Vaccine efficacy % (95% CI)
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Primary analysis population					
Participants who had 2 doses of VAXZEVRIA & were seronegative at baseline & followed ≥15 days after the 2nd dose [a]	8,597	84 (0.98)	8,581	248 (2.89)	66.73 (57.41, 74.01)
Licensing regimen					
Participants who had 2 doses of the standard dose & were followed for ≥15 days after the 2nd dose.	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

[a] Some of the participants in this group received an initial LD. These were included in the primary analysis as the immune response in this group was similar to that in the SD and efficacy would therefore be expected to be the same. However, when this subgroup was analysed, the efficacy was greater. There are many factors other than having a LD that may have influenced the results (including lower age, longer duration between doses), thus the use of a LD will not be considered further for regulatory purposes. Two doses of vaccine are required.

The level of protection gained from a single dose of VAXZEVRIA 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, vaccine efficacy from 22 days post-dose 1 was 71.42% (95% CI: 51.11; 84.08 [VAXZEVRIA 18/9,335 vs control 63/9,312]).

An exploratory analyses of the impact of duration between doses and efficacy demonstrated greater efficacy with increasing duration between vaccine doses (Table 4). This was supported by the immunogenicity data (see Table 6).

Table 4 Vaccine efficacy for incidence of first SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥15 days post second dose by dose interval (SDSD seronegative for efficacy analysis set) in the pivotal Oxford clinical trials (COV001, COV002, COV003 and COV005)

Dose interval	Participants with events, n (%)				Vaccine efficacy (%)	95% CI (%)
	N	VAXZEVRIA n (%)	N	Control n (%)		
< 6 weeks	3890	35 (0.90)	3856	76 (1.97)	55.10	(33.00, 69.91)
6–8 weeks	1112	20 (1.80)	1009	44 (4.36)	59.92	(32.01, 76.37)
9–11 weeks	906	11 (1.21)	958	32 (3.34)	63.65	(27.96, 81.66)
≥12 weeks	1293	8 (0.62)	1356	45 (3.32)	81.31	(60.31, 91.20)

Vaccine efficacy (VE) of VAXZEVRIA versus control and the 95% CI were estimated based on Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset.

VE is defined as 1-(incidence from the VAXZEVRIA arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

The observation period for the endpoint was 15 days post second dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events are adjudicated events based on virologically-confirmed results from RT-PCR or other nucleic acid amplification test; COVID-19 includes all PCR-confirmed SARS-CoV-2 events with primary symptoms or WHO grade ≥ 4.

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

VAXZEVRIA reduced COVID-19 hospitalisation (WHO Severity grading ≥4).

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 VAXZEVRIA 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 in sub-groups

Participants who had one or more mild 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 VAXZEVRIA (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 VAXZEVRIA (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 VAXZEVRIA (N=945) compared to 13 for control (N=896), with 0 vs 2 cases in the VAXZEVRIA and control groups, respectively, leading to hospitalisation (WHO severity grading ≥4.

Analysis of efficacy data from Study D8110C00001

VAXZEVRIA has been evaluated based on an analysis (data lock: 5 March 2021) from a randomised, double blinded, placebo-controlled Phase III trial conducted in the United States, Peru and Chile. The trial randomised 32,451 healthy adults or those with medically-stable chronic diseases ≥18 years of age. The study excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with severe immunosuppression. All participants are planned to be followed for up to 1 year for assessments of efficacy against COVID-19 disease.

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

Baseline demographics were balanced across the VAXZEVRIA and the placebo groups. Of the participants who received VAXZEVRIA, 79.1% were aged 18 to 64 years and 20.9% were ≥65 years of age; 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, 0.3% were Native Hawaiian or Other Pacific Islander, and 2.4% were of multiple races (1.7% were unknown or not reported). A total of 10,376 (58.8%) participants who received VAXZEVRIA versus 5,105 (59.7%) who received placebo had at least one pre-existing comorbidity. At the time of analysis the median follow up time post-dose 2 was 61 days.

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

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

Category A: One or more of the following

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

Category B: Two or more of the following:

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

VAXZEVRIA significantly decreased the incidence of COVID 19 compared to placebo (see Table 5).

Table 5 VAXZEVRIA efficacy against COVID-19 (Study D8110C00001)[a]

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

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

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

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

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

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

[e] 97.5% CI

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

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

Efficacy in sub-groups

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

In participants ≥65 years old who had received VAXZEVRIA (≥15 days post-dose 2; N=3,696), there were 5 (0.1%) cases of COVID-19 compared to 14 (0.8%) cases for placebo (N=1,812), corresponding to a vaccine efficacy of 83.5% [95% CI: 54.17, 94.06].

Updated efficacy analyses

In the 6-month follow-up analysis (data lock: 30 July 2021), updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, with a median follow-up time post second dose of 78 days in participants who received VAXZEVRIA and 71 days in participants who received placebo. Overall vaccine efficacy against symptomatic COVID-19 illness in subjects without prior evidence of SARS-CoV-2 infection was 66.98% (95% CI: 58.87, 73.50) with 141 (0.80%) cases of COVID-19 reported in participants who had received two doses of VAXZEVRIA (N=17,617) and 184 (2.16%) cases reported in participants who had received placebo (N=8,528). In participants ≥65 years old there were 6 (0.16%) cases reported in the VAXZEVRIA group (N=3,696) compared with 19 (1.05%) cases in the placebo group (N=1,816), corresponding to a vaccine efficacy of 86.35% (95% CI: 65.79, 94.55).

In individuals with or without prior evidence of SARS-CoV-2 infection, vaccine efficacy against symptomatic COVID-19 illness was 66.96% (95% CI: 58.94, 73.41) with 144 (0.78%) versus 189 (2.11%) cases of COVID-19 in the VAXZEVRIA (N=18,450) and placebo (N=8,960) groups, respectively.

Against severe or critical symptomatic COVID-19 illness, vaccine efficacy was 95.69% (95% CI: 66.33, 99.45) with 1 (0.01%) case reported in the VAXZEVRIA group (N=17,617) and 10 (0.12%) cases reported in the placebo group (N=8,528). There were 2 (0.01%) versus 15 (0.18%) cases of COVID-19-related emergency department visits in the VAXZEVRIA (N=17,617) and placebo (N=8,528) groups, respectively, corresponding to a vaccine efficacy of 94.17% (95% CI: 74.49, 98.67).

The prevention of SARS-CoV-2 infection (symptomatic and asymptomatic) was evaluated by the occurrence of SARS-CoV-2 nucleocapsid antibodies ≥15 days post second dose. In the 6-month follow-up analysis, there were 295 (1.67%) SARS-CoV-2 infections in the VAXZEVRIA group (N=17,617) and 323 (3.79%) infections in the placebo group (N=8,528), corresponding to a vaccine efficacy of 61.01% (95% CI: 54.35; 66.70).

Immunogenicity data in individuals receiving 2 doses (primary analysis of pooled data from the pivotal Oxford clinical trials - COV001, COV002, COV003, and COV005)

An immunological correlate of protection has not been established; therefore the level of immune response that provides protection against COVID-19 is unknown.

Following vaccination with VAXZEVRIA, 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 (see Table 6).

Generally similar trends were observed between analyses of neutralising antibodies and S-binding antibodies.

Table 6 SARS-CoV-2 S-binding antibody response to VAXZEVRIA (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) 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)
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 6).

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 14 days after a first dose of VAXZEVRIA. 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 VAXZEVRIA with cells expressing IFN-γ, IL-2, and/or TNFα which are generally similar between age categories.

Efficacy of a third dose of VAXZEVRIA

No data has been evaluated regarding the efficacy of a third dose of VAXZEVRIA in preventing clinically evident COVID-19 infection or severe COVID-19 illness.

Study D7220C00001, immunogenicity of a booster dose following primary vaccination with VAXZEVRIA or an mRNA COVID-19 vaccine

D7220C00001 is a phase II/III partially double-blind, active-controlled study in which 367 participants ≥30 years old previously vaccinated with VAXZEVRIA and 322 participants ≥30 years old previously vaccinated with an mRNA vaccine received a single booster dose of VAXZEVRIA at least 90 days after receiving the second dose of their primary vaccination course. Immunogenicity was assessed in 342 participants previously vaccinated with VAXZEVRIA and 294 participants previously vaccinated with an mRNA vaccine, all of whom were seronegative at baseline.

The effectiveness of VAXZEVRIA administered as a single booster dose in participants previously vaccinated with VAXZEVRIA was demonstrated by evaluating non-inferiority of the immune response of pseudoneutralising antibody titres against the ancestral strain compared to that elicited by a 2-dose primary vaccination course in a subset of matched participants in Study D8110C00001.

Non-inferiority for GMT ratio was demonstrated when comparing pseudoneutralising antibody titres 28 days after the booster dose to titres 28 days after the primary vaccination course (see Table 7).

Table 7 Pseudoneutralising antibody titres against the ancestral strain following booster dosing with VAXZEVRIA in participants previously vaccinated with VAXZEVRIA

	28 days after primary vaccination course with VAXZEVRIA[a]	28 days after booster dose	GMT ratio[b]	Met non-inferiority objective (Y/N)
n	508	327	327/508	
GMT [c]	242.80	248.89	1.03	Y[d]
(95% CI)	(224.82, 262.23)	(229.53, 269.89)	(0.92, 1.15)	

n = Number of subjects in analysis; GMT = Geometric mean pseudoneutralising antibody titre; CI = Confidence interval; GMT Ratio = Geometric mean titre ratio

[a] Based on analyses from a matched cohort of participants in Study D8110C00001

[b] GMT 28 days after booster dose to GMT 28 days after the second dose of the primary vaccination course

[c] Reported results have been adjusted using an ANCOVA model including fixed-effect terms for visit window, time since previous vaccination (for booster), baseline comorbidities, sex, age and a random subject effect.

[d] Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio of the comparator group and the reference group is >0.67

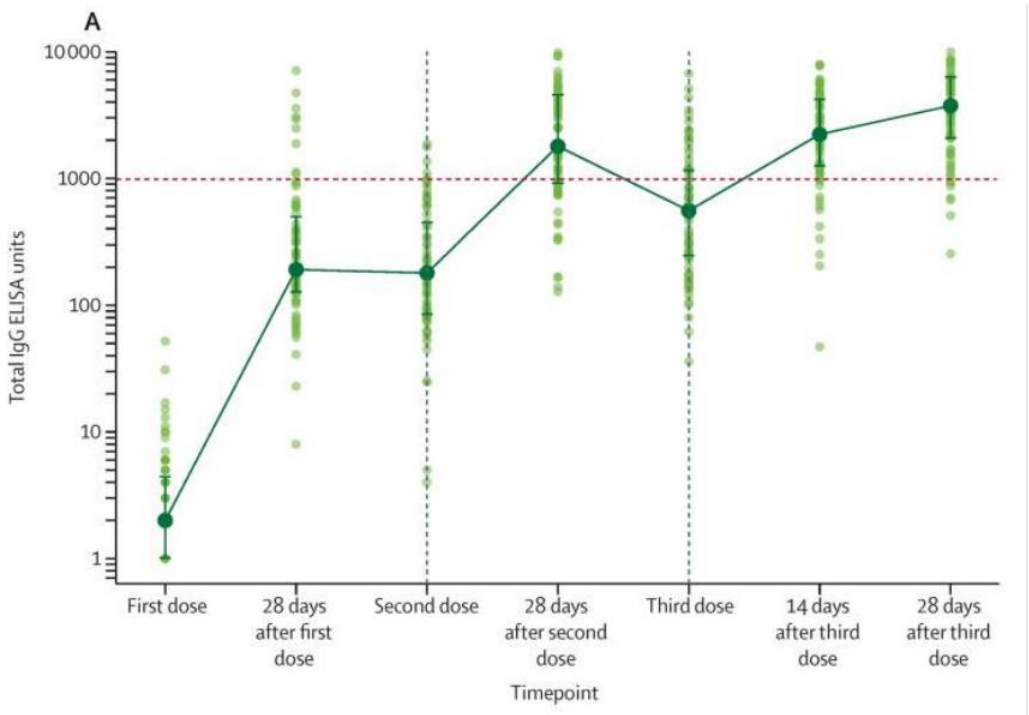
VAXZEVRIA was also shown to be effective in eliciting antibody responses in participants who had previously received primary vaccination with an mRNA vaccine. In these participants, a single booster dose of VAXZEVRIA resulted in increased humoral responses, with geometric mean fold rise (GMFR) of 3.77 (95% CI: 3.26, 4.37) in pseudoneutralising antibody titres against the ancestral strain from pre-booster to 28 days after the booster dose.

COV001 immunogenicity of a third (booster) dose following primary vaccination with VAXZEVRIA

COV001 included 90 participants aged 18-55 years who received a third (booster) dose with VAXZEVRIA. Antibody responses were assessed in 75 participants who had received their two doses of the primary vaccination course within an 8-16 week interval, followed by a third (booster) dose administered between 28-38 weeks after the second dose. There was a statistically significant increase in spike IgG antibody titres after the third dose from a median of 1792 EU [IQR 899–4634] at 28 days after the second dose to 3746 EU [IQR 2047–6420] 28 days after the third dose; pairwise comparison in 73 participants for whom samples were available using Wilcoxon signed rank test; p=0.0043).

The relative efficacy of VAXZEVRIA as a third (booster) dose compared to other vaccines as boosters is not known. It is noted that the incremental increase in antibody concentrations is lower following a third (booster) dose with ChAdOx1-S than following mRNA vaccines in published studies.

Figure 1 Antibody responses in participants who received a third dose of VAXZEVRIA



Antibody levels to SARS-CoV-2 Victoria/01/2020 spike protein measured by total IgG ELISA (n=75). Datapoints in lighter colours represent individual participants and darker datapoints show median values with error bars showing the IQRs and with solid lines connecting these median values.

Source: Figure 5A in Flaxman et al 2021

Efficacy in emerging SARS-CoV-2 variants

Limited data are available on the impact of emerging SARS-CoV-2 variants of concern on vaccine efficacy. Further information will be collected throughout the VAXZEVRIA clinical development program by clinical and surveillance virology monitoring.

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

VAXZEVRIA is a vaccine, as such, genotoxicity (mutagenicity) studies have not been conducted.

Carcinogenicity

VAXZEVRIA is a vaccine, as such, carcinogenicity studies have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

VAXZEVRIA contains the excipients histidine, histidine hydrochloride monohydrate, sodium chloride, magnesium chloride hexahydrate, disodium edetate (EDTA), sucrose, ethanol absolute, polysorbate 80 and water for injections.

VAXZEVRIA does not contain any preservatives and the vial stopper is not made with natural rubber latex.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened multidose vial

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Store in outer carton in order to protect from light.

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 to 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 (2ºC to 8ºC) 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).

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 30°C, or
- 48 hours in a refrigerator (2°C to 8°C)

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

See Section 4.2 Dose and method of administration/Method of administration for details on the storage of the vaccine in syringes.

6.5 NATURE AND CONTENTS OF CONTAINER

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

VAXZEVRIA contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in accordance with local requirements in a clinical waste bin. Spills should be disinfected with an appropriate antiviral disinfectant.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

2420395-83-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

16 February 2021

10 DATE OF REVISION

17 April 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Section updated with later duration of follow-up pooled date safety outcomes including revised Table 1 adverse reactions. Includes new adverse reaction (decreased appetite) and increased frequency adverse reactions (dizziness and abdominal pain)
5.1	Minor editorial amendments to the introduction text in the *Primary analysis of pooled data from COV001, COV002, COV003, and COV005* section
8	Contact details revised to the standard AstraZeneca contact details

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