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28 April 2023

Dear Healthcare Professional,

CONDITIONAL REGISTRATION OF VAXZEVRIA SOLUTION FOR INJECTION WITH EXEMPTIONS FROM MALAYSIA SPECIFIC LABELLING REQUIREMENTS

With regards to the matter above, AstraZeneca would like to inform that the approval in Malaysia is supported by common pack product label and carton to facilitate supply during pandemic period. In order to make the artwork acceptable to multiple countries around the world during the pandemic the artwork is exempted from a number of country specific labelling requirements. There will not be country-specific packs for Malaysia until the post pandemic period which has not been determined yet.

2. The name and address for the Marketing Authorization Holder (MAH) in EU, AstraZeneca AB, SE-151 85 Sodertalje Sweden, is reflected on the product carton.

3. Enclosed are the additional Malaysian local labelling information for your reference which will not be included in the artwork during the pandemic period.

Immediate label

Product Information	**Details**
Product Name	Vaxzevria Solution for Injection
Strength of active substance	1 x 10^11 vp/ml
Name and content of alcohol	Ethanol 2 mg per 0.5 ml dose

Outer Carton

Product Information	**Details**
Storage Condition	Store in a refrigerator (2 to 8°C). Do not freeze. Keep vials in outer carton in order to protect from light.
Name and content of alcohol	This medicinal product contains 2 mg of alcohol (ethanol) per 0.5 ml dose.
Disposal	Vaxzevria 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.
Keep out of the sight and reach of children	Jauhi dari pandangan dan jangkauan kanak-kanak
Strength of active substance	1 x 10^11 vp/ml
Batch Releaser	AstraZeneca Nijmegen BV Lagelandseweg 78 6545 CG Nijmegen The Netherlands
Local Registration Number (MAL Number)	MAL21036009ACZ

Product Registration Holder (PRH)	AstraZeneca Sdn Bhd (69730-X) Level 11 & 12, The Bousteador, No. 10, Jalan PJU 7/6, Mutiara Damansara, 47800 Petaling Jaya, Selangor, Malaysia
Others	Controlled Medicine

4. Any future labelling updates will be submitted to the National Pharmaceutical Regulatory Division (NPRA) for review and approval before implementation on packs.

Thank you.

Yours sincerely,
Faziatul Amira Binti Mat Isa
Regulatory Affairs
AstraZeneca Sdn. Bhd.

DISCLAIMER: THIS PRODUCT IS APPROVED UNDER MALAYSIA CONDITIONAL REGISTRATION FOR PHARMACEUTICAL PRODUCTS DURING DISASTER GUIDELINE. THE ADMINISTRATION OF THE PRODUCT IS PURELY BASED ON INDIVIDUAL'S PREFERENCE

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 new or serious adverse reactions.

This product information will be updated on a regular basis as further data and safety reports become available.

1. NAME OF THE MEDICINAL PRODUCT

Vaxzevria Solution for Injection
COVID-19 Vaccine (ChAdOx1-S [recombinant])

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:
COVID-19 Vaccine (ChAdOx1-S* recombinant) 5×10^{10} viral particles (vp)
*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

This product contains genetically modified organisms (GMOs).

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

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

Individuals 18 years of age and older

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 (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.

A booster dose of 0.5 ml Vaxzevria may be administered at least 3 months after the second dose of Vaxzevria or another authorised COVID-19 vaccine (see section 4.8 and 5.1) when the potential benefits outweigh any potential risks.

The decision when and for whom to implement a booster dose of the vaccine should be made based on available vaccine effectiveness data, taking into account limited safety data (see clinical section).

Elderly population

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

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.

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.

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

4.4 Special warnings and 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

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. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to the previous 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.

Coagulation disorders

- *Thromboembolism in combination with 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-authorisation use. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of the events occurred within the first 21 days following vaccination. The reporting rates after the second dose are lower compared to after the first dose. See also section 4.3. Healthcare professionals should consult applicable guidance and, if available, seek advice from specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

  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.

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

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

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 confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences

spontaneous bleeding, skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention

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.

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.

Neurological events

Very rare events of demyelinating disorders, including Guillain-Barré syndrome (GBS), have been reported following vaccination with Vaxzevria. A causal relationship has not been established.

As with other vaccines, the benefits and potential risks of vaccinating individuals with Vaxzevria should be considered.

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.

Interchangeability

There are limited safety, immunogenecity and efficacy data available regarding the interchangeability of Vaxzevria with other COVID-19 vaccines. For the available data on the use of Vaxzevria as a booster dose following primary vaccination with another COVID-19 vaccine, see sections 4.8 and 5.1.

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

Data from more than 400 case reports of pregnant women or women who became pregnant after receiving Vaxzevria do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed.

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 may be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with Vaxzevria. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed (see section 5.3). It is unknown whether the vaccine itself is excreted in human milk. In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

Available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants.

Fertility

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

4.7 Effects on ability to drive and use machines

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

Primary vaccination course

The overall safety of Vaxzevria is based on an analysis of pooled data from four clinical studies phase I/II, II/III and III conducted in the United Kingdom, Brazil, and South Africa, and of data from an additional phase III clinical study conducted in the United States, Peru and Chile. At the time of the analysis, a total of 56,124 participants ≥18 years old had been randomised and of these, 33,869 received at least one dose of Vaxzevria and 31,217 received two doses.

The most frequently reported adverse reactions are injection site tenderness (68%), injection site pain (58%), headache (53%), fatigue (53%), myalgia (44%), malaise (44%), pyrexia (includes feverishness

[33%] and fever ≥38°C [8%]), chills (32%), arthralgia (27%) and nausea (22%). The majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.

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

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 older adults (≥65 years old).

The safety profile was consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline.

Booster dose (third dose)

In study D7220C00001, 367 participants who had previously received a 2-dose primary vaccination course with Vaxzevria, and 322 participants who had previously received a 2-dose primary vaccination course with an mRNA vaccine received a single booster dose (third dose) of Vaxzevria. The safety profile observed in participants who received a booster dose (third dose) was consistent with the known safety profile of Vaxzevria. The reactogenicity observed in participants who had previously received primary vaccination with an mRNA vaccine was similar to the reactogenicity observed in participants receiving a first dose of Vaxzevria in previous clinical studies.

In the COV001 study, the observed reactogenicity in the 80 participants who received a booster dose (third dose) following a 2-dose primary vaccination course with Vaxzevria was consistent with the known reactogenicity profile of Vaxzevria, and was lower after the third dose compared with after the first dose.

In the externally sponsored study RHH-001, 304 participants received a single booster dose (third dose) of Vaxzevria following a 2-dose primary vaccination course with an inactivated whole-virion SARS-CoV-2 vaccine. The reported reactogenicity profile was consistent with the known reactogenicity 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.

Tabulated list of adverse reactions

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

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). 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); 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]

MedDRA SOC	Frequency	Adverse Reactions
	Uncommon	Lymphadenopathy
	Not known	Immune thrombocytopenia[b]
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Nervous system disorders	Very common	Headache[c]
	Uncommon	Dizziness Somnolence Lethargy Paraesthesia Hypoesthesia
	Rare	Facial paralysis[d]
	Very rare	Guillain-Barré syndrome
	Not known	Transverse myelitis
Ear and labyrinth disorders	Uncommon	Tinnitus
Vascular disorders	Very rare	Thrombosis in combination with thrombocytopenia[e]
	Not known	Capillary leak syndrome Cerebrovascular venous and sinus thrombosis[b]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting Diarrhoea
	Uncommon	Abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis Pruritus Rash Urticaria
	Not known	Angioedema Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
	Common	Pain in extremity
	Uncommon	Muscle spasms
General disorders and administration site conditions	Very common	Injection site tenderness, pain, warmth, pruritus, bruising[f] Fatigue Malaise Feverishness Chills
	Common	Injection site swelling, erythema Fever[g] Influenza-like illness Asthenia

[a] In clinical trials, transient mild trombocytopenia was commonly reported (see section 4.4).
[b] Cases have been reported post-marketing (see also section 4.4).
[c] Headache includes migraine (uncommon).[d] Based on data from the clinical study conducted in the United States, Peru and Chile. Through the safety follow-up period to 05 March 2021, facial paralysis (or palsy) was reported by five participants in the Vaxzevria group. Onset was 8 and 15 days after first dose and 4, 17, and 25 days after the second dose. All events were reported to be non-serious. No cases of facial paralysis were reported in the placebo group.
[e] 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).
[f] Injection site bruising includes injection site haematoma (uncommon).
[g] Measured fever ≥38°C.

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 NPRA website and include batch/Lot number if available.

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.

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/m^2, 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 ≥37.8°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 in COV002 and COV003[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%) 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 weeks interval after the first dose (see section 4.4).

Analysis of data from Study D8110C00001

The clinical efficacy of Vaxzevria has been evaluated based on an analysis of Study D8110C00001: a randomised, double-blinded, placebo-controlled phase III study conducted in the United States, Peru and Chile. The study excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with severe immunosuppression, pregnant women and participants with a known history of SARS-CoV-2 infection. All participants are planned to be followed for up to 12 months, for assessments of efficacy against COVID-19 disease.

Participants ≥18 years of age received two doses (5×10^{10} viral particles per dose corresponding to not less than 2.5×10^{8} infectious units) of Vaxzevria (N=17,662) or saline placebo (N=8,550), administered via IM injection on Day 1 and Day 29 (-3 to +7 days). The median dose interval was

29 days and the majority of participants (95.7% and 95.3% for Vaxzevria and placebo, respectively) received the second dose ≥26 to ≤36 days after dose 1.

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

Final determination of COVID-19 cases were made by an adjudication committee. Overall vaccine efficacy and efficacy by key age groups are presented in Table 3.

Table 3 – Vaxzevria efficacy against symptomatic COVID-19 illness in Study D8110C00001

	Vaxzevria			Placebo			Vaccine efficacy % (95% CI)[b]
	N	Number of COVID-19 cases[a], n (%)	Incidence rate of COVID-19 per 1,000 person-years	N	Number of COVID-19 cases[a], n (%)	Incidence rate of COVID-19 per 1,000 person-years	
Overall (age ≥18 years old)	17,662	73 (0.4)	35.69	8,550	130 (1.5)	137.23	74.0 (65.3, 80.5)
Age 18 to 64 years old	13,966	68 (0.5)	40.47	6,738	116 (1.7)	148.99	72.8 (63.4, 79.9)
Age ≥65 years old	3,696	5 (0.1)	13.69	1,812	14 (0.8)	82.98	83.5 (54.2, 94.1)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event;
CI = Confidence Interval.
[a] Symptomatic COVID-19 requiring positive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and at least 1 respiratory sign or symptom, or at least 2 other systemic signs or symptoms, as defined in the protocol.
[b] The confidence intervals were not adjusted for multiplicity.

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

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

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

In the 6-month follow-up analysis, updated efficacy analyses were performed with additional

confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, with a median follow-up of 78 days in participants who received Vaxzevria and 71 days in participants who received placebo. Overall vaccine efficacy against symptomatic COVID-19 illness was 67.0% (95% CI: 58.9, 73.5) with 141 (0.8%) cases of COVID-19 reported in participants who had received two doses of Vaxzevria (N=17,617) and 184 (2.2%) cases reported in participants who had received placebo (N=8,528). In participants aged 18 to 64 years there were 135 (1.0%) cases in the Vaxzevria group (N=13,921) versus 165 (2.5%) cases in the placebo group (N=6,712), corresponding to a vaccine efficacy of 64.8% (95% CI: 55.7, 71.9). In participants ≥65 years old vaccine efficacy was 86.3% (95% CI: 65.8, 94.6) with 6 (0.2%) cases in the Vaxzevria group (N=3,696) versus 19 (1.1%) cases in the placebo group (N=1,816).

Immunogenicity

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 ≥18 years old previously vaccinated with Vaxzevria and 322 participants ≥18 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. Participants previously vaccinated with Vaxzevria were older than participants previously vaccinated with an mRNA vaccine with 45.9% and 26.9% being ≥65 years of age in the two groups, respectively. Approximately 47% of the participants had at least one pre-existing comorbidity (defined as BMI ≥30 kg/m^2, significant cardiovascular disease, chronic lung disease, or diabetes).

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 neutralising 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 neutralising antibody titres 28 days after the booster dose to titres 28 days after the primary vaccination course (see Table 4).

Table 4: Neutralising 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 neutralising 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 neutralising antibody titres against the ancestral strain from pre-booster to 28 days after the booster dose.

Booster dosing with Vaxzevria increased humoral responses also in participants with serological evidence of prior SARS-CoV-2 infection at baseline, and against all analysed variants, i.e. Alpha, Beta, Gamma, Delta and Omicron.

COV001 Immunogenicity of a booster dose (third dose) following primary vaccination with Vaxzevria

COV001 included 90 participants aged 18-55 years who received a 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 weeks interval, followed by a booster dose administered between 28-38 weeks after the second dose. Spike IgG antibody titres after the booster dose were significantly higher than after the second dose (median total IgG titre was 1792 EUs [IQR 899–4634] at 28 days after the second dose vs 3746 EUs [2047–6420] 28 days after the booster dose; pairwise comparison in 73 participants for whom samples were available using Wilcoxon signed rank test; p=0.0043).

RHH-001 immunogenicity of a booster dose (third dose) following primary vaccination with an inactivated whole-virion COVID-19 vaccine

The externally sponsored RHH-001 was a phase IV single-blind, randomised study, in which antibodies were assessed in 296 Brazilian participants >18 years old who received a booster dose of Vaxzevria 5-7 months after receiving the second dose of an inactivated whole-virion COVID-19 vaccine.

At 28 days after receipt of a booster dose of Vaxzevria there was a substantial increase from baseline in spike IgG antibody titres (Day 28 GMT, 335213 [95% CI: 295598, 380136], baseline GMT 3745 [95% CI: 3252, 4313]). The GMFR from baseline to Day 28 was 90 (95%, CI: 77, 104). Participants who had received a booster dose of Vaxzevria had spike IgG antibody titres at Day 28 that were statistically superior to those induced by a booster dose of the inactivated whole-virion COVID-19 vaccine. Geometric mean ratio (GMR) for Vaxzevria booster dose versus the inactivated COVID-19 vaccine booster dose was 7.0 (95% CI 6.1, 8.1, p<0,0001). Booster dosing with Vaxzevria also increased neutralisation antibody titres against the Delta and Omicron variants.

Elderly population

Study D8110C00001 assessed the efficacy of Vaxzevria in 5,508 individuals ≥65 years of age; 3,696 who received Vaxzevria and 1,812 who received placebo. The efficacy of Vaxzevria was consistent between elderly (≥65 years) and younger adult subjects (18-64 years).

Paediatric population

See section 4.2 for information on paediatric use.

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

Biodistribution studies conducted in mice did not show measurable distribution of Vaxzevria to the gonads (testes, ovaries) following IM injection.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate
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 (86°F)
- 72 hours down to -3°C (27°F)

Unopened vials must always be returned to refrigerated storage (2 to 8ºC [36 to 46°F]) 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 vial

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

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

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

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

Unopened multidose vial
Store in a refrigerator (2 to 8°C).
Do not freeze.
Keep vials in outer carton to protect from light.

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

6.5 Nature and contents of container

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

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 solution. Discard

the vial if the solution is discoloured or visible particles are observed. Do not shake. Do not dilute the solution.

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.

The vaccine does not contain any preservative. After first opening, use the vial within:

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

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

Disposal

Vaxzevria contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in compliance with the local guidance for genetically modified organisms or biohazardous waste. Spills should be disinfected using agents with activity against adenovirus.

7. MANUFACTURER

AstraZeneca Nijmegen BV
Lagelandseweg 78
6545 CG Nijmegen
The Netherlands

8. DATE OF REVISION OF THE TEXT

September 2023
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