SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One dose (0.5 mL) contains:
Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)[*], not less than 2.5×10^8 infectious units (Inf.U)
[*]Produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology.

This product contains genetically modified organisms (GMOs).

Excipient with known effect
Each dose (0.5 mL) contains approximately 2 mg of ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Posology

Individuals 18 years of age and older
The Vaxzevria 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).

A booster dose (third dose) of 0.5 mL may be given to individuals who completed the primary vaccination course with Vaxzevria or an approved mRNA COVID-19 vaccine (see sections 4.8 and 5.1). The third dose should be administered at least 3 months after completing the primary vaccination course.

Elderly population
No dose adjustment is required. See also section 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.

Individuals who have experienced thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria (see section 4.2).

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to a 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

- ***Thrombosis with thrombocytopenia syndrome:*** Thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following

vaccination with Vaxzevria. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first three weeks following vaccination. The reporting rates after the second dose are lower compared to after the first dose. See also section 4.3.
TTS requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

- ***Cerebrovascular venous and sinus thrombosis:*** Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been observed very rarely following vaccination with 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 after receiving 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. Cases with fatal outcome have been reported. If an individual has a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination.

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

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

Risk of bleeding with intramuscular administration
As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Capillary leak syndrome

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

Neurological events

Guillain-Barré syndrome (GBS) and transverse myelitis (TM) have been reported very rarely following vaccination with Vaxzevria. Healthcare professionals should be alert of GBS and TM signs

and symptoms 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 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 studies.

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).

Excipients

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 mL dose, that is to say essentially “sodium-free”.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Vaxzevria with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

Breastfeeding

It is unknown whether Vaxzevria is excreted in human milk.

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

Fertility

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

4.7 Effects on ability to drive and use machines

Vaxzevria has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

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 the population of 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)

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 mRNA COVID-19 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.

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]
	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
	Rare	Facial paralysis[d]
	Very rare	Guillain-Barré syndrome
	Not known	Transverse myelitis
Vascular disorders	Very rare	Thrombosis with thrombocytopenia syndrome[e]
	Not known	Capillary leak syndrome Cerebrovascular venous and sinus thrombosis[b]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting Diarrhoea

MedDRA SOC	Frequency	Adverse Reactions
	Uncommon	Abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis Pruritus Rash Urticaria
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
	Common	Pain in extremity
	Uncommon	Muscle spasms
General disorders and administration site conditions	Very common	Injection site tenderness, pain, warmth, pruritus, bruising[f] Fatigue Malaise Feverishness Chills
	Common	Injection site swelling, erythema Fever[g] Influenza-like illness Asthenia

[a] In clinical studies, transient mild thrombocytopenia 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 national reporting system and include batch/Lot number if available.

4.9 Overdose

There is no specific treatment for an overdose with Vaxzevria. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Vaxzevria is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The

SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralising antibody and cellular immune responses, which may contribute to protection to COVID-19.

Clinical efficacy

Analysis of 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 2.

Table 2. 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).

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 studies: 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 3).

Table 3. Vaxzevria efficacy against COVID-19 from 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%) cases of COVID-19 for Vaxzevria (N=2,068) and control (N=2,040), respectively; which was similar to the vaccine efficacy observed in the overall population.

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

Immunogenicity after booster dose

Study D7220C00001, immunogenicity of a booster dose (third 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 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.

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

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

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

In a repeat-dose toxicity study in mice, IM administration of Vaxzevria was well tolerated. Non-adverse, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve consistent with the anticipated findings after IM injection of vaccines. There were no findings in the administration sites or sciatic nerves at the end of the recovery period, indicating complete recovery of the Vaxzevria-related inflammation.

Genotoxicity/Carcinogenicity

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

Reproductive toxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

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

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

The shelf-life of unopened vials includes the following unforeseen excursions from refrigerated storage (2°C – 8°C) for a single period of:
- 12 hours up to 30°C
- 72 hours down to -3°C

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

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

Opened vial

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

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

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

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Multidose vial

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

10-dose vial
5 mL of solution in a 10-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal). Each vial contains 10 doses of 0.5 mL. Pack sizes of 10 multidose vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions and administration

This vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

Do not use this vaccine after the expiry date which is stated on the label after EXP.

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.

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

Disposal

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

7. DATE OF REVISION OF THE TEXT

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