Summary of the risk management plan for COVID-19 Vaccine AstraZeneca (ChAdOx1-S/AZD1222)

Introduction

This document is a summary of the risk management plan (RMP) for COVID-19 Vaccine AstraZeneca (ChAdOx1-S/AZD1222). The RMP was created by the vaccine manufacturer and is submitted to medicine regulators as part of the vaccine approval and safety monitoring processes.

The RMP details the important risks of COVID-19 Vaccine AstraZeneca and how they can be minimised. It also describes how more information will be obtained about these risks and any uncertainties (missing information). The RMP will be updated as more information becomes available, including any new risks or changes to current ones.

The COVID-19 Vaccine AstraZeneca data sheet, consumer medicine information and the package leaflet give essential information for healthcare professionals and patients on how to use the vaccine.

See also the European Public Assessment Report (EPAR), including the risk management plan, available on the European Medicines Agency website (note, the vaccine is called Vaxzevria in Europe).

RMP definitions

Important risks

Important risks need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks are classified as identified or potential.

- Identified risks are concerns for which there is sufficient proof of a link with the use of the medicine.
- Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Activities to minimise or further characterise identified risks

Measures to minimise the identified risks for medicinal products may include:

- specific information for healthcare professionals and patients, such as warnings, precautions and advice on correct use, in the data sheet, consumer medicine information and package leaflet
- important advice on the medicine's packaging

- the authorised pack size − the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- the medicine's legal status − the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously by the company and regularly analysed, so that immediate action can be taken by the company as necessary. These measures constitute *routine pharmacovigilance activities*.

Other non-routine measures to further characterise the risks include safety and efficacy studies. The studies may be in particular risk groups or for particular safety concerns. They may also be a condition of the medicine's approval. These measures constitute *additional pharmacovigilance activities*.

COVID-19 Vaccine AstraZeneca RMP

The medicine and what it is used for

COVID-19 Vaccine AstraZeneca is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. It contains Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S) as the active substance, and it is given by intramuscular injection only, preferably in the deltoid muscle.

Further information about the evaluation of COVID-19 Vaccine AstraZeneca's benefits can be found in COVID-19 Vaccine AstraZeneca's EPAR (note, the vaccine is called Vaxzevria in Europe), including in its plain-language summary, available on the European Medicines Agency website.

Important risks, missing information and additional pharmacovigilance activities

The tables below summarise the risks for COVID-19 Vaccine AstraZeneca, as described in the RMP.

- Table 1 is a list of the important risks (identified and potential) and missing information.
- Tables 2–14 provide the evidence for linking the risk to the medicine, risk factors and risk groups, risk minimisation measures and a list of additional pharmacovigilance activities.
- Table 15 summarises the additional pharmacovigilance activities (studies) and Table 16 summarised a list of other studies.

Table 1: List of important risks and missing information

Important identified risks	Thrombosis with thrombocytopenia syndrome Thrombocytopenia, including immune thrombocytopenia Guillain-Barré syndrome Anaphylaxis
Important potential risks	Thrombosis Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use during pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interactions with other vaccines Long-term safety

Table 2: Important identified risk: Thrombosis with thrombocytopenia syndrome

Evidence for linking the risk to the medicine	Very rare events of serious thrombosis with thrombocytopenia syndrome (TTS) (including fatal events), have been observed following vaccination with AZD1222 during post-authorisation use. There have been no reports of TTS in the AZD1222 clinical development programme.
Risk factors and risk groups	There are no known risk factors for the development of thrombosis with thrombocytopenia following vaccination.
Risk minimisation measures	Data sheet sections 4.3, 4.4. and 4.8 Consumer medicine information leaflet
Additional pharmacovigilance activities*	Interventional study in immunocompromised adults (D8111C00010) Biodistribution study (1169DM) In vitro expression of Spike protein HIT antibodies in vaccinated sera In vitro interaction with PF4 and/or platelets Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Table 3: Important identified risk: Thrombocytopenia, including immune thrombocytopenia

Evidence for linking the risk to the medicine	Very rare cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been observed following vaccination with AZD1222 during post-authorisation use
Risk factors and risk groups	There are no known risk factors for the development of thrombocytopenia following vaccination. In general, individuals with a history of 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 as described in Section 4.4 of the data sheet.
Risk minimisation measures	Data sheet sections 4.4 and 4.8 Consumer medicine information leaflet
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Table 4: Important identified risk: Guillain-Barré syndrome (GBS)

Evidence for linking the risk to the medicine	In a US study, there was 1 serious adverse event (SAE) of a demyelinating event: a participant in the AZD1222 group had an adverse event (AE) initially reported as Guillain-Barré syndrome , which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy. Very rare events of GBS have been observed following vaccination with AZD1222 during post-authorisation use.
Risk factors and risk groups	There are no known risk factors for the development of GBS following vaccination. In general, infection with the bacteria *Campylobacter jejuni* is one of the most common risk factors for GBS. People also can develop GBS after having the flu or other infections such as cytomegalovirus and Epstein-Barr virus. On very rare occasions, people develop GBS in the days or weeks after getting a vaccination (Centers for Disease Control and Prevention. 2019. Guillain-Barre Syndrome and Vaccines. URL: cdc.gov/vaccinesafety/concerns/guillain-barre-syndrome.html).
Risk minimisation measures	Data sheet sections 4.4 and 4.8 Consumer medicine information leaflet
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Table 5: Important identified risk: Anaphylaxis

Evidence for linking the risk to the medicine	The risk of anaphylaxis is idiosyncratic in nature, with anaphylaxis risk after all vaccines estimated to be 1.31 (95% confidence interval: 0.90–1.84) per million vaccine doses. No serious or acute events of anaphylaxis were reported in AZD1222 clinical trials, and therefore the risk of anaphylaxis is a theoretical concern based on data from other vaccines (as a class of medications). There were no serious reports of anaphylaxis, and no reported acute allergic reactions in the AZD1222 clinical development programme. Very rare events of anaphylaxis have been observed following vaccination with AZD1222 during post-authorisation use.
Risk factors and risk groups	Almost all components of a vaccine (including excipients) may be considered as potential triggers of an allergic reaction, and therefore known hypersensitivity to any component of AZD1222 and/or a history of allergic reactions are considered to be risk factors for the development of anaphylaxis.
Risk minimisation measures	Data sheet sections 4.3, 4.4. and 4.8 Consumer medicine information leaflet
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Table 6: Important potential risk: Thrombosis

Evidence for linking the risk to the medicine	Very rare events of serious thrombosis have been observed following vaccination with AZD1222 during post authorisation use. Overall, there have been no clinically meaningful imbalances in the incidence of events of thrombosis between the AZD1222 and control groups in the AZD1222 clinical development programme.
Risk factors and risk groups	There are no known risk factors identified for the development of thrombosis following vaccination.
Risk minimisation measures	Data sheet section 4.4
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Table 7: Important potential risk: Nervous system disorders, including immune-mediated neurological conditions

Evidence for linking the risk to the medicine	The association between vaccines and acute demyelinating events has been assessed in a range of studies and expert reviews, including a population-based analysis of nearly 64 million vaccine doses in the United States, which concluded that if there is an association between transverse myelitis and vaccines, it is <2 per million doses of live-zoster and live-attenuated influenza vaccines, and <1 per million doses for other vaccines. Moreover, demyelinating diseases occur more frequently with infections than with vaccination. Taken together, the evidence is inconclusive regarding a causal relation between contemporary vaccines and acute demyelinating events. Overall, there have been no clinically meaningful imbalances in the incidence of neurological adverse events of special interest (AESIs) between the AZD1222 and control groups in the AZD1222 clinical development programme. Very rare events of immune-mediated neurological conditions have been observed following vaccination with AZD1222 during post-authorisation use.
Risk factors and risk groups	There are no known risk factors for the development of neurological conditions following vaccination.
Risk minimisation measures	Consumer medicine information leaflet
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Table 8: Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Evidence for linking the risk to the medicine	There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED/VAERD. Vaccine-associated enhanced disease was observed in children given formalin-inactivated whole-virus vaccines against respiratory syncytial virus and measles virus, and findings from experimental models of SARS-CoV and MERS-CoV infection suggest that VAED/VAERD may be possible in certain conditions. Overall, there is no evidence of an association between AZD1222 and VAED/VAERD; proportionally more AESIs related to COVID-19 have occurred in the control/placebo groups than among AZD1222 recipients in the AZD1222 clinical development programme. There have been no confirmed post-marketing reports of VAED/VAERD.
Risk factors and risk groups	There are no known risk factors identified for VAED/VAERD.
Risk minimisation measures	None
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Table 9: Missing information: Use during pregnancy and while breastfeeding

Risk minimisation measures	Data sheet section 4.6, consumer medicine information leaflet
Additional pharmacovigilance activities*	Pregnancy Registry (D8110C00003) Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU])

* See Table 15 for a summary of the studies.

Table 10: Missing information: Use in immunocompromised patients

Risk minimisation measures	Data sheet section 4.4 Consumer medicine information leaflet
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources Interventional study in immunocompromised patients (D8111C00010) Study COV005

* See Table 15 for a summary of the studies.

Table 11: Missing Information: Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	None
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU])

* See Table 15 for a summary of the studies.

Table 12: Missing Information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	None
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU])

* See Table 15 for a summary of the studies.

Table 13: Missing Information: Interaction with other vaccines

Risk minimisation measures	Data sheet section 4.5 Consumer medicine information leaflet
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU])

* See Table 15 for a summary of the studies.

Table 14: Missing Information: Long-term safety data

Risk minimisation measures	None
Additional pharmacovigilance activities*	Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002

* See Table 15 for a summary of the studies.

Studies

Table 15: Summaries of the COVID-19 Vaccine AstraZenenca (AZD1222 / ChAdOx1 nCoV-19) studies listed in Tables 2–14

1169DM: AZD1222 (ChAdOx1-nCovd-19): A Single Dose Intramuscular Vaccine Biodistribution Study in the Mouse To determine the biodistribution of AZD1222 when given by single intramuscular injection to mice to further characterise the possible mechanisms and to identify the possible triggers of platelet activation after vaccination.
COV001: A Phase I/II Study to Determine Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers This study was initiated as the first-in-human study employing candidate vaccine AZD1222 (ChAdOx1 nCoV-19). The primary objectives of this study are to assess the efficacy and safety of AZD1222 against COVID-19.
COV002: Phase II/III Study to Determine the Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 The primary objectives of this study are to assess efficacy and safety of AZD1222 (ChAdOx1 nCoV-19) against COVID-19 in adults aged 18 years and older in the UK.
COV003: A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine The primary objective of this study is to evaluate the efficacy of AZD1222 against COVID-19 disease confirmed with polymerase chain reaction (PCR).
COV004: A Phase IB/II Single-Blinded, Randomised, Controlled Study to Determine Safety, Immunogenicity and Efficacy of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in Adults in Kenya The primary objectives of this study are to assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19; and to assess immunogenicity of ChAdOx1 nCoV-19

COV005: An Adaptive Phase I/II Randomised Placebo-controlled Trial to Determine Safety, Immunogenicity and Efficacy of Non-Replicating ChAdOx1 SARS-CoV-2 Vaccine in South African Adults Living Without HIV; and Safety and Immunogenicity in Adults Living with HIV The primary objectives of this study in the HIV-uninfected participants group are to assess the safety, tolerability and reactogenicity profile of AZD1222; and to assess the efficacy of AZD1222 against all-severity COVID-19.
D8110C00001: A Phase III Randomized, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19 The primary objectives of this study are to estimate the efficacy of 2 intramuscular (IM) doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥18 years of age; to assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥18 years of age; and to assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥18 years of age (Substudy only).
D8110C00003: Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy as part of the C-VIPER Registry Consortium The study objective is to estimate the risk of the most common obstetric outcomes (pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19), neonatal outcomes (congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID- 19), and infant outcomes (height for age, weight for height, developmental milestones until one year of age, and COVID-19) among pregnant women exposed to AZD1222 from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group
D8111C00002: Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19 The primary objectives of this study are to assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo; and to assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222.
D8111C00010: Immunogenicity and Safety Study of AZD1222 Vaccine in Immunocompromised Adults To characterise the immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults
D81110R00002 [US] / D8111R00006 [EU/UK]: A post-authorisation/post-marketing observational study to evaluate the association between exposure to AZD1222 and safety concerns using existing secondary health data sources The study objective is to evaluate the incidence and relative risk of safety concerns and adverse events of special interest (AESIs).
Are HIT antibodies increased in the sera of vaccinated individuals To test sera of vaccinated individuals for the presence of such antibodies to further characterise the possible mechanisms and to identify the possible triggers of platelet activation after vaccination
In vitro expression of spike protein following transduction by AZD1222 To address the question of spike expression by cells transduced by AZD1222 to further characterize the possible mechanisms and to identify the possible triggers of platelet activation after vaccination

In vitro interaction of AZD1222 or spike protein with PF4 and/or platelets To test the interaction of AZD1222 or spike protein with PF4 or platelets to further characterise the possible mechanisms and to identify the possible triggers of platelet activation after vaccination
Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency, in order to provide additional data to support the characterisation of the area of missing information of 'Use in immunocompromised patients'.

Table 16: Other studies

An assessment of a relationship between the exposure to COVID-19 vaccines and risk of thrombotic thrombocytopenia syndrome To investigate the association of vaccine exposure with venous thrombotic events and thrombocytopenia using multiple study design approaches.
Evaluation of effectiveness of AZD1222 in the United Kingdom To evaluate the effectiveness of AZD1222 in England using National Health Service data
D8111R00005 [EU/UK] / D8110R00003 [US]: A post-authorization/post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care The primary objective is to estimate brand specific vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among (primarily) hospitalized patients, overall and by age group (eg, < 18, 18 to 64 and ≥ 65 years old), after adjusting for potential confounders.