Summary of the risk management plan (version 1.2) for COVID-19 Vaccine Janssen (Ad26.COV2.S)

Introduction

This document is a summary of the risk management plan (RMP) for COVID-19 Vaccine Janssen (Ad26.COV2.S). 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 Janssen (Ad26.COV2.S) and how they can be minimised. It also describes how more information will be obtained about these risks and any uncertainties (missing information). The vaccine manufacturer will update the RMP as more information becomes available, including any new risks or changes to current ones.

The COVID-19 Vaccine Janssen (Ad26.COV2.S) data sheet, consumer medicine information (CMI) and the package leaflet give essential information for healthcare professionals and patients on how to use the vaccine.

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 Janssen (Ad26.COV2.S) RMP

The medicine and what it is used for

COVID-19 Vaccine Janssen (Ad26.COV2.S) is a monovalent vaccine for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older (see the data sheet for the full indication). The vaccine contains Ad26.COV2.S as the active substance and it is given by intramuscular injection.

Important risks, missing information and additional pharmacovigilance activities

The tables below summarise the risks for COVID-19 Vaccine Janssen (Ad26.COV2.S), as described in the RMP.

- Table 1 is a list of the important risks (identified and potential) and missing information.
- Tables 2–10 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 11 summarises the additional pharmacovigilance activities.

Table 1: List of important risks and missing information

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD) Venous thromboembolism
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Interaction with other vaccines Long-term safety

Table 2: Important identified risk: Anaphylaxis

Evidence for linking the risk to the medicine	Allergic reactions, including possibly severe reactions (eg, hypersensitivity reactions and anaphylaxis), are known to occur with any injectable vaccine. COVID-19 Vaccine Janssen (Ad26.COV2.S) contains ingredients with known potential to cause allergic reactions, including polysorbate 80. The structure of polysorbate 80 presents similarities with polyethylene glycol, recently suspected to be involved in anaphylactic reactions with mRNA vaccines.
Risk factors and risk groups	Participants with a known history of hypersensitivity to any component of the vaccine may be at risk for hypersensitivity reactions.
Additional pharmacovigilance activities*	Trial VAC31518COV3001 Trial VAC31518COV3009 Study VAC31518COV4003 Study VAC31518COV4001

*See Table 11 for a summary of the studies

Table 3: Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD)

Evidence for linking the risk to the medicine	VAERD was first seen in the 1960s in infants with respiratory syncytial virus (RSV) infection after receiving a vaccine against RSV that led to markedly worse respiratory disease as compared to non-vaccinated infants. Subsequently, reports of VAED were reported in individuals without prior exposure to Dengue who received tetravalent Dengue vaccines. Non-clinical experience with severe acute respiratory syndrome coronavirus (SARS-CoV) – and Middle East respiratory syndrome coronavirus-based vaccines also indicated a risk for VAERD, however, this risk could not be confirmed in humans due to the lack of efficacy studies. For candidate SARS-CoV-2 vaccines, no evidence of VAED or VAERD has been reported to date in nonclinical studies or clinical trials. Nevertheless, in the absence of long-term safety and efficacy data, the evidence is not yet sufficient to fully dismiss VAED, including VAERD as a safety concern, and it remains an important potential risk.
Risk factors and risk groups	It is postulated that the potential risk may be increased in individuals producing lower neutralising antibody titres or in those demonstrating waning immunity.
Additional pharmacovigilance activities*	Trial VAC31518COV3001 Trial VAC31518COV3009 Study VAC31518COV4004 Study VAC31518COV4002

*See Table 11 for a summary of the studies

Table 4: Important potential risk: Venous thromboembolism

Evidence for linking the risk to the medicine	Natural infection with SARS-COV-2 has shown to be associated with hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and venous thromboembolism (VTE) or arterial thrombosis. The hypercoagulable state observed in patients with severe COVID-19 is thought to be related to the high-grade systemic inflammatory response, although other mechanisms such as the higher incidence of severe COVID-19 in individuals with risk factors for thrombotic and thromboembolic events have been proposed. It is unknown whether these proposed mechanisms linking COVID-19 and thromboembolic events could also be applicable for vaccines against COVID-19.
Risk factors and risk groups	In the general population, important intrinsic factors for the onset of deep vein thrombosis (DVT) and pulmonary embolism (PE) include a prior medical or family history of DVT or PE, venous insufficiency, heart disease, obesity, long periods of standing position, and multiparity. Important triggering factors for a DVT/PE event include pregnancy, trauma or a violent effort, deterioration of the general condition, immobilisation, long distance travel, and infection. On the other hand, transverse sinus thrombosis is a disease more commonly observed in children and young adults. Important risks factors for transverse sinus thrombosis include thrombophilia, trauma, puerperium, and chronic inflammatory diseases. In addition, patients with transverse sinus stenosis have a strong risk for thrombosis, usually misdiagnosed as idiopathic intracranial hypertension.

Additional pharmacovigilance activities*	Trial VAC31518COV3001 Trial VAC31518COV3009 Study VAC31518COV4003 Study VAC31518COV4001 Trial VAC31518COV2001

*See Table 11 for a summary of the studies

Table 5: Missing information: Use in pregnancy and while breastfeeding

Additional pharmacovigilance activities*	Trial VAC31518COV3001 (This trial will only address use while breastfeeding) Trial VAC31518COV3009 (This trial will only address use while breastfeeding) Trial VAC31518COV2004 Study VAC31518COV4005 (This study will only address use in pregnancy)

*See Table 11 for a summary of the studies

Table 6: Missing information: Use in immunocompromised patients

Risk minimisation measures	Routine risk minimisation measures: • Data sheet section 4.4 • CMI section 2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities*	Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients Study VAC31518COV4003 Study VAC31518COV4004 Study VAC31518COV4001 Study VAC31518COV4002

*See Table 11 for a summary of the studies

Table 7: Missing information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	Routine risk minimisation measures: • None Additional risk minimisation measures: • None
Additional pharmacovigilance activities*	Study VAC31518COV4003 Study VAC31518COV4001

*See Table 11 for a summary of the studies

Table 8: Missing information: Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	Routine risk minimisation measures: • None Additional risk minimisation measures: • None
Additional pharmacovigilance activities*	Trial VAC31518COV3001 Study VAC31518COV4003 Study VAC31518COV4001

*See Table 11 for a summary of the studies

Table 9: Missing information: Interaction with other vaccines

Risk minimisation measures	Routine risk minimisation measures: • None • CMI section 2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities*	Coadministration study of Ad26.COV2.S with seasonal influenza vaccine

*See Table 11 for a summary of the studies

Table 10: Missing information: Long-term safety data

Risk minimisation measures	Routine risk minimisation measures: • None Additional risk minimisation measures: • None
Additional pharmacovigilance activities*	Trial VAC31518COV3001 Trial VAC31518COV3009 Study VAC31518COV4003 Study VAC31518COV4001

*See Table 11 for a summary of the studies

Table 11: Additional pharmacovigilance activities

Study	**Purpose of the study**
VAC31518COV3001	A randomised, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. To evaluate the efficacy safety, reactogenicity, and immunogenicity of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.
VAC31518COV3009	A randomised, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. To evaluate the efficacy, safety, reactogenicity, and immunogenicity of 2 doses of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.

VAC31518COV2004	An open-label, Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in healthy pregnant participants. To assess the safety, reactogenicity, and immunogenicity of Ad26.COV2.S in adult participants during the 2nd and/or 3rd trimester of pregnancy, to assess the safety and reactogenicity of Ad26.COV2.S (potentially) post-partum, and to assess pregnancy outcomes. To assess the presence of immunoglobulins against SARS-CoV-2 in colostrum and breast milk.
Interventional trial to evaluate the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients	To assess the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients.
VAC31518COV4005	COVID-19 Vaccines International Pregnancy Exposure Registry (CVIPER). To assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy.
VAC31518COV4003	Post-authorisation, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe. To assess the occurrence of pre-specified adverse events of special interest (AESIs) within specific risk periods following administration of Ad26.COV2.S.
VAC31518COV4004	Post-authorisation, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe. To estimate the effectiveness of Ad26.COV2.S in preventing laboratory confirmed SARS-CoV-2 hospitalisations up to 2 years post-vaccination.
VAC31518COV4001	Post-authorisation, observational study to assess the safety of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States. To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.
VAC31518COV4002	Post-authorisation, observational study to assess the effectiveness of Ad26.COV2.S using health insurance claims and/or electronic health record (EHR) database(s) in the United States. To estimate the effectiveness of Ad26.COV2.S in preventing medically attended COVID-19 up to 2 years post-vaccination.

Coadministration study of Ad26.COV2.S with seasonal influenza vaccine	To assess the safety and immunogenicity of Ad26.COV2.S and seasonal influenza vaccine when administered separately or concomitantly.
VAC31518COV2001	A randomised, double-blind, placebo-controlled Phase 2a study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults aged 18 to 55 years inclusive and adults aged 65 years and older and to evaluate 2 dose levels of Ad26.COV2.S in healthy adolescents aged 12 to 17 years inclusive. To evaluate the efficacy, safety, reactogenicity, and immunogenicity of Ad26.COV2.S at different dose levels and as a 2-dose or a 1-dose schedule.