COVID-19 Vaccine Janssen
COVID-19 vaccine (Ad26.COV2-S [recombinant])

Risk Management Plan

Summary of Activities in the Risk Management Plan (RMP)

for COVID-19 Vaccine Janssen (Ad26.COV2-S)

Document Version 1.0

Version Number of the Current RMP: 1.4

Name of the Marketing Authorisation Holder: Janssen-Cilag AG Document

Date: 11 March 2021

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of COVID-19 Vaccine Janssen is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of COVID-19 Vaccine Janssen in Switzerland is the "Arzneimittleinformation / Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of COVID-19 Vaccine Janssen.

Summary of Risk Management Plan for COVID-19 Vaccine Janssen

This is a summary of the risk management plan (RMP) for COVID-19 Vaccine Janssen. The RMP details important risks of COVID-19 Vaccine Janssen, how these risks can be minimized, and how more information will be obtained about COVID-19 Vaccine Janssen's risks and uncertainties (missing information).

COVID-19 Vaccine Janssen's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how COVID-19 Vaccine Janssen should be used.

This summary of the RMP for COVID-19 Vaccine Janssen should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of COVID-19 Vaccine Janssen's RMP.

I. The Vaccine and What it is Used For

COVID-19 Vaccine Janssen is authorised for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older (see SmPC for the full indication). It contains Ad26.COV2.S as the active substance and it is given by intramuscular injection.

Further information about the evaluation of COVID-19 Vaccine Janssen's benefits can be found in COVID-19 Vaccine Janssen's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the vaccine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen.

II. Risks Associated With the Vaccine and Activities to Minimize or Further Characterize the Risks

Important risks of COVID-19 Vaccine Janssen, together with measures to minimize such risks and the proposed studies for learning more about COVID-19 Vaccine Janssen's risks, are outlined below.

Measures to minimize the risks identified for vaccines can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to individuals and healthcare professionals;
- Important advice on the vaccine's packaging;
- The authorised pack size — the amount of vaccine in a pack is chosen so to ensure that the vaccine is used correctly;
- The vaccine's legal status — the way a vaccine is supplied to the individual (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of COVID-19 Vaccine Janssen is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of COVID-19 Vaccine Janssen are risks that need special risk management activities to further investigate or minimize the risk, so that the vaccine can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of COVID-19 Vaccine Janssen. Potential risks are concerns for which an association with the use of this vaccine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the vaccine that is currently missing and needs to be collected (eg, on the long-term use of the vaccine).

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

II.B. Summary of Important Risks

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 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. The potential for polysorbate 80 to trigger hypersensitivity and the possibility of cross-reactivity between polyethylene glycol and polysorbate 80 have been discussed in the literature. Cases of polysorbate 80-induced hypersensitivity have been reported and have involved different drugs, including a human papillomavirus vaccine, and different routes of administration, including the intramuscular route. After the data lock point of this EU-RMP, severe allergic reactions and one case of anaphylaxis have been identified following vaccination with COVID-19 Vaccine Janssen. All of these events occurred in the context of an open-label study in South Africa. Anaphylaxis is an adverse drug reaction described in the SmPC.
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.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • SmPC Section 4.4 and PL Section 3 provide recommendations to address the risk of anaphylaxis. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3001 • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.

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. Nonclinical 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 neutralizing antibody titers or in those demonstrating waning immunity.
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3001 • Trial VAC31518COV3009 • Study VAC31518COV4004 • Study VAC31518COV4002 See section II.C of this summary for an overview of the post-authorisation development plan.
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 occurrence of thrombotic and thromboembolic events in context of coronavirus disease-2019 (COVID-19) is associated with a poor outcome. 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, immobilization, 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. In trial COV3001, the following risk factors have been identified in participants with VTE: male gender, old age (>65 years), long-haul travel, thrombophilia, obesity, hypertension, and COPD. SARS-COV-2 infection is also considered an important risk factor, with 2 participants (1 per study group) having a positive polymerase chain reaction test. Anatomical malformations were also found to be risk factors for cranial venous thrombotic events.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3001 • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 • Trial VAC31518COV2001 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Use in pregnancy and while breastfeeding	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.6 (only for use in pregnancy) • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	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) • Study VAC31518COV4003 (The adequacy of the study to address pregnancy outcomes is to be assessed. The safety of Ad26.COV2.S in breastfeeding women will not be studied.) See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in immunocompromised patients	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	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 section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Use in patients with autoimmune or inflammatory disorders	
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3001 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Interaction with other vaccines	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.5 • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Coadministration study of Ad26.COV2.S with seasonal influenza vaccine See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Long-term safety	
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Trial VAC31518COV3001 • Trial VAC31518COV3009 • Study VAC31518COV4003 • Study VAC31518COV4001 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorisation

VAC31518COV3001: A randomized, 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.

Purpose of the study: To evaluate the efficacy safety, reactogenicity, and immunogenicity of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19.

II.C.2. Other Studies in Post-authorisation Development Plan

VAC31518COV3009: A randomized, 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.

Purpose of the study: 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.

Purpose of the study: 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.

Purpose of the study: To assess the safety and immunogenicity of Ad26.COV2.S in immunocompromised patients.

VAC31518COV4005: COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER).

Purpose of the study: To assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy.

VAC31518COV4003: Post-authorization, observational study to assess the safety of Ad26.COV2.S using electronic health record (EHR) database(s) in Europe.

Purpose of the study: 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-authorization, observational, prospective study to assess the effectiveness of Ad26.COV2.S in Europe.

Purpose of the study: To estimate the effectiveness of Ad26.COV2.S in preventing laboratory-confirmed SARS-CoV-2 hospitalizations up to 2 years post-vaccination.

VAC31518COV4001: Post-authorization, 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.

Purpose of the study: To assess the occurrence of pre-specified AESIs within specific risk periods following administration of Ad26.COV2.S.

VAC31518COV4002: Post-authorization, 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.

Purpose of the study: 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

Purpose of the study: To assess the safety and immunogenicity of Ad26.COV2.S and seasonal influenza vaccine when administered separately or concomitantly.

VAC31518COV2001: A randomized, 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.

Purpose of the study: 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.