Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multi-dose vial which contains 5 doses of

0.5 mL. One dose (0.5 mL) contains:
Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein* (Ad26.COV2-S), not less than
2.5×10^{10} virus particles of Ad26.COV2-S or not less than 8.92 $\log_{10}$ infectious units (Inf.U).
* Produced in the PER.C6 TetR Cell Line and by recombinant DNA

technology. The product contains genetically modified organisms

(GMOs).

Excipients 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

Suspension for injection (injection).

Colourless to slightly yellow, clear to very opalescent suspension (pH 6-6.4).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Individuals 18 years of age and older

Primary vaccination

COVID-19 Vaccine Janssen is administered as a single-dose of 0.5 mL by intramuscular injection only.

Booster dose

A booster dose (second dose) of 0.5 mL of COVID-19 Vaccine Janssen may be administered intramuscularly at least 2 months after the primary vaccination in individuals 18 years of age and older (see also sections 4.4, 4.8 and 5.1).

A booster dose of the COVID-19 Vaccine Janssen (0.5 mL) may be administered in individuals 18 years of age and older as a heterologous booster dose following completion of primary vaccination with an mRNA COVID-19 vaccine, an adenoviral vector-based COVID-19 vaccine or an inactivated whole-virion COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as that authorised for a booster dose of the vaccine used for primary vaccination (see also sections 4.4, 4.8 and 5.1).

Paediatric population

The safety and efficacy of COVID-19 Vaccine Janssen in children and adolescents (less than 18 years of age) have not yet been established. No data are available.

Elderly

No dose adjustment is required in elderly individuals ≥65 years of age. See also

sections 4.8 and 5.1. Method of administration

COVID-19 Vaccine Janssen is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, intravenously, 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 of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

A history of confirmed thrombosis with thrombocytopenia syndrome (TTS) following vaccination with any COVID-19 vaccine (see also section 4.4).

Individuals who have previously experienced episodes of capillary leak syndrome (CLS) (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 reaction following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination.

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:*** A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination. Thrombosis in combination with thrombocytopenia 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.

Individuals who have experienced thrombosis with thrombocytopenia syndrome following vaccination with any COVID-19 vaccine should not receive COVID-19 Vaccine Janssen (See also section 4.3).

- ***Venous thromboembolism:*** Venous thromboembolism (VTE) has been observed rarely following vaccination with COVID-19 Vaccine Janssen (see section 4.8). This should be considered for individuals at increased risk for VTE.
- ***Immune thrombocytopenia:*** Cases of immune thrombocytopenia with very low platelet levels (<20,000 per µL) have been reported very rarely after vaccination with COVID-19 Vaccine Janssen, usually within the first four weeks after receiving COVID-19 Vaccine Janssen. This included cases with bleeding and cases with fatal outcome. Some of these cases occurred in individuals with a history of immune thrombocytopenia (ITP). If an individual has a history of ITP, the risks of developing low platelet levels should be considered before vaccination, and platelet monitoring is recommended after vaccination.

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

Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with COVID-19 Vaccine Janssen should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 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 COVID-19 Vaccine Janssen, in some cases with a fatal outcome. A history of CLS 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

Guillain-Barré syndrome and transverse myelitis

Guillain-Barré syndrome (GBS) and transverse myelitis (TM) have been reported very rarely following vaccination with COVID-19 Vaccine Janssen. Healthcare professionals should be alert to 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.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with JCOVDEN (section 4.8). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often in males younger than 40 years of age.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat these conditions.

Risk of severe adverse events after a booster dose

The risk of severe adverse events (such as coagulation disorders including thrombosis with thrombocytopenia syndrome, CLS, GBS, myocarditis and pericarditis) after a booster dose of COVID- 19 Vaccine Janssen 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 COVID-19 Vaccine Janssen may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

Protection starts around 14 days after vaccination. As with all vaccines, vaccination with COVID-19 Vaccine Janssen 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 COVID-19 Vaccine Janssen with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with the use of COVID-19 Vaccine Janssen in pregnant women. Animal studies with COVID-19 Vaccine Janssen do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development (see section 5.3).

Administration of COVID-19 Vaccine Janssen in pregnancy should only be considered when the potential benefits outweigh any potential risks to the mother and foetus.

Breast-feeding

It is unknown whether COVID-19 Vaccine Janssen is excreted in

human milk. Fertility

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

4.7 Effects on ability to drive and use machines

COVID-19 Vaccine Janssen 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 safety profile

Primary vaccination (primary pooled analysis)

The safety of COVID-19 Vaccine Janssen was evaluated in the primary pooled analysis from the double-blind phase of the randomised, placebo-controlled studies COV1001, COV1002, COV2001, COV3001 and COV3009. A total of 38538 adults aged 18 years and older received at least a single- dose primary vaccination of

COVID-19 Vaccine Janssen. The median age of individuals was 52 years (range 18-100 years). For the primary pooled analysis, the median follow-up for individuals who received COVID-19 Vaccine Janssen was approximately 4 months after completion of primary vaccination. Longer safety follow-up of ≥ 6 months is available for 6136 adults who received COVID- 19 Vaccine Janssen.

In the primary pooled analysis, the most common local adverse reactions reported was injection site pain (54.3%). The most common systemic adverse reactions were fatigue (44.0%), headache (43.0%), myalgia (38.1%) and nausea (16.9%). Pyrexia (defined as body temperature ≥ 38.0°C) was observed in 7.2% of participants. Most adverse reactions were mild to moderate in severity. Across the studies, most adverse reactions occurred within 1–2 days following vaccination and were of short duration (1– 2 days).

Reactogenicity was generally milder and reported less frequently in older adults.

The safety profile was generally consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline. A total of 10.6% of individuals that received COVID-19 Vaccine Janssen were SARS-CoV-2 positive at baseline (based on serology or RT-PCR assessment).

Booster dose (second dose) following primary vaccination with COVID-19 Vaccine Janssen

The safety of a booster dose (second dose) with COVID-19 Vaccine Janssen administered approximately 2 months after the primary vaccination was evaluated in an ongoing randomised, double-blind, placebo-controlled Phase 3 Study (COV3009). In the FAS (full analysis set), from the 15708 adults aged 18 years and older who received 1 dose of COVID-19 Vaccine Janssen, a total of 8646 individuals received a second dose during the double-blind phase.

The safety of a booster dose (second dose) with COVID-19 Vaccine Janssen administered at least 6 months after the primary vaccination was evaluated in a randomised, double-blind Phase 2 Study (COV2008 Cohort 1 N=330).

Overall, the solicited adverse reaction profile for the homologous booster dose was similar to that after the first dose. There were no new safety signals identified.

Booster dose following primary vaccination with an mRNA COVID-19 vaccine

Overall, in 3 clinical studies (including 2 independent studies) approximately 500 adults have received primary vaccination with 2 doses of an mRNA COVID 19 vaccine and received a single booster dose of COVID-19 Vaccine Janssen, at least 3 months after primary vaccination (COV2008, COV-BOOST and DMID 21-0012 studies). There were no new safety concerns identified. However, a trend towards an increase in frequency and severity of solicited local and systemic adverse events after the heterologous booster dose was observed when compared with the homologous booster dose of COVID-19 Vaccine Janssen.

Booster dose following primary vaccination with an adenoviral vector-based COVID-19

vaccine

The safety of a heterologous booster dose of COVID-19 Vaccine Janssen was evaluated in the COV- BOOST study following primary vaccination with an adenoviral vector-based COVID-19 vaccine.
Participants received 2 doses of Vaxzevria (N=108) followed by a booster dose of COVID-19 Vaccine Janssen 77 days post second dose (median; IQR: 72-83 days). There were no new safety concerns identified.

Booster dose following primary vaccination with an inactivated whole-virion COVID-19 vaccine

The safety of a heterologous booster dose of COVID-19 Vaccine Janssen was evaluated in the RHH- 001 study, an independent, randomised Phase 4 study (RBR-9nn3scw) conducted at 2 sites in Brazil following primary vaccination with an inactivated whole-virion COVID-19 vaccine. Participants were adults 18 years of age or older that had received 2 doses of CoronaVac (N=305) followed by a booster dose of COVID-19 Vaccine Janssen, and were 182 days (plus or minus 30 days) post second dose at the time of boost. Adverse events were assessed through 28 days after the booster dose. There were no new safety concerns identified.

Tabulated list of adverse reactions

Adverse drug reactions observed in the primary pooled analysis or from post marketing sources are organised by MedDRA System Organ Class (SOC).
Frequency categories are defined as follows: Very common (≥ 1/10);
Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1000 to < 1/100); Rare (≥ 1/10000 to < 1/1000); Very rare (< 1/10000);
Not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported following vaccination with COVID-19 Vaccine Janssen

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)	Very Rare (< 1/10000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Lymph-adenopathy		Immune thrombo-cytopenia

Immune system disorders				Urticaria; hypersensitivity[a]		Anaphylaxis[b]
Nervous system disorders	Headache		Dizziness; tremor	Paraesthesia; hypoaesthesia; facial paralysis (including Bell's palsy)	Guillain - Barré syndrome	Transverse myelitis
Ear and labyrinth disorders				Tinnitus		
Cardiac disorders						Myocarditis, pericarditis
Vascular disorders				Venous thromboembolism	Thrombosis in combination with thrombo-cytopenia	Capillary leak syndrome; cutaneous small vessel vasculitis
Respiratory, thoracic and mediastinal disorders			Cough; oropharyngeal pain; sneezing			
Gastrointestinal disorders	Nausea		Diarrhoea; vomiting			
Skin and subcutaneous tissue disorders			Rash	Hyperhidrosis		
Musculoskeletal and connective tissue disorders	Myalgia		Arthralgia; muscular weakness; back pain; pain in extremity			

General disorders and administration site conditions	Injection site pain; fatigue	Pyrexia; injection site erythema; injection site swelling; chills	Malaise; asthenia			

[a] Hypersensitivity refers to allergic reactions of the skin and subcutaneous tissue.
[b] Cases received from an ongoing open-label study in South Africa.

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

No case of overdose has been reported. In Phase 1/2 studies where a higher dose (up to 2-fold) was administered COVID-19 Vaccine Janssen remained well-tolerated, however vaccinated individuals reported an increase in reactogenicity (increased vaccination site pain, fatigue, headache, myalgia, nausea and pyrexia).

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: COVID-19, viral vector, non-replicating, ATC code:

J07BN02 Mechanism of action

COVID-19 Vaccine Janssen is a monovalent vaccine composed of a recombinant, replication- incompetent human adenovirus type 26 vector that encodes a SARS-CoV-2 full-length spike (S) glycoprotein in a stabilised conformation. Following administration, the S glycoprotein of
SARS-CoV-2 is transiently expressed, stimulating both neutralising and other functional S-specific antibodies, as well as cellular immune responses directed against the S antigen, which may contribute to protection against COVID-19.

Clinical efficacy

Efficacy from a single-dose primary

vaccination Primary analysis

A primary analysis (cut-off date 22 January 2021) of a multicentre, randomised, double-blind, placebo-controlled Phase 3 study (COV3001) was conducted in the United States, South Africa and Latin American countries to assess the efficacy, safety, and immunogenicity of a single-dose primary vaccination of COVID-19 Vaccine Janssen for the prevention of COVID-19 in adults aged 18 years and older. The study excluded individuals with abnormal function of the immune system resulting from a clinical condition, individuals who are under immunosuppressive therapies within 6 months, as well as pregnant women. Participants with stable HIV infection under treatment were not excluded.

Licensed vaccines, excluding live vaccines, could be administered more than 14 days before or more than 14 days after the vaccination in the study. Licensed live attenuated vaccines could be administered more than 28 days before or more than 28 days after the vaccination in the study.

A total of 44325 individuals were randomised in parallel in a 1:1 ratio to receive an intramuscular injection of COVID-19 Vaccine Janssen or placebo. A total of 21895 adults received COVID-19 Vaccine Janssen and 21888 adults received placebo. Participants were followed for a median follow- up of approximately 2 months after vaccination.

The primary efficacy analysis population of 39321 individuals included 38059 SARS-CoV-2 seronegative individuals at baseline and 1262 individuals with an unknown serostatus.

Demographic and baseline characteristics were similar among individuals who received the COVID-19 Vaccine Janssen and those who received placebo. In the primary efficacy analysis population, among the individuals who received COVID-19 Vaccine Janssen, the median age was
52.0 years (range: 18 to 100 years); 79.7% (N=15646) of individuals were 18 to 64 years old [with 20.3% (N=3984) aged 65 or older and 3.8% (N=755) aged 75 or older]; 44.3% of individuals were female; 46.8% were from Northern America (United States), 40.6% were from Latin America and 12.6% were from Southern Africa (South Africa). A total of 7830 (39.9%) individuals had at least one pre-existing comorbidity associated with increased risk of progression to severe COVID-19 at baseline (Comorbidities included: obesity defined as BMI ≥30 kg/m^2 (27.5%), hypertension (10.3%), type 2 diabetes (7.2%), stable/well-controlled HIV infection (2.5%), serious heart conditions (2.4%) and asthma (1.3%)). Other comorbidities were present in ≤1% of the individuals.

COVID-19 cases were confirmed by a central laboratory based on a positive SARS-CoV-2 viral RNA result using a polymerase chain reaction (PCR)-based test. Vaccine efficacy overall and by key age groups are presented in Table 2.

Table 2: Analysis of vaccine efficacy against COVID-19[b] in SARS-CoV-2 seronegative adults - primary efficacy analysis population after a single-dose

Subgroup	COVID-19 Vaccine Janssen N=19630		Placebo N=19691		% Vaccine Efficacy (95% CI)[c]
	COVID-19 Cases (n)	Person-	COVID-19 Cases (n)	Person-	

		Years		**Years**	
14 days post-vaccination					
All subjects[a]	116	3116.6	348	3096.1	66.9 (59.0; 73.4)
18 to 64 years of age	107	2530.3	297	2511.2	64.2 (55.3; 71.6)
65 years and older	9	586.3	51	584.9	82.4 (63.9; 92.4)
75 years and older	0	107.4	8	99.2	100 (45.9; 100.0)
28 days post-vaccination					
All subjects[a]	66	3102.0	193	3070.7	66.1 (55.0; 74.8)
18 to 64 years of age	60	2518.7	170	2490.1	65.1 (52.9; 74.5)
65 years and older	6	583.3	23	580.5	74.0 (34.4; 91.4)
75 years and older	0	106.4	3	98.1	–

[a] Co-primary endpoint as defined in the protocol.
[b] Symptomatic COVID-19 requiring positive RT-PCR result and at least 1 respiratory sign or symptom or 2 other systemic signs or symptoms, as defined in the protocol.
[c] Confidence intervals for 'All Subjects' were adjusted to implement type I error control for multiple testing. Confidence intervals for age groups are presented unadjusted.

Vaccine efficacy against severe COVID-19 is presented in Table 3 below.

Table 3: Analyses of vaccine efficacy against severe COVID-19[a] in SARS-CoV-2 seronegative adults - primary efficacy analysis population after a single-dose

Subgroup	COVID-19 Vaccine Janssen N=19630		Placebo N=19691		% Vaccine Efficacy (95% CI)[b]
	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	
14 days post-vaccination					
Severe	14	3125.1	60	3122.0	76.7 (54.6; 89.1)
28 days post-vaccination					
Severe	5	3106.2	34	3082.6	85.4 (54.2; 96.9)

[a] Final determination of severe COVID-19 cases was made by an independent adjudication committee, who also assigned disease severity according to the definition per FDA guidance.
[b] Confidence intervals were adjusted to implement type I error control for multiple testing.

Of the 14 vs. 60 severe cases with onset at least 14 days after vaccination in the COVID-19 Vaccine Janssen group vs. placebo group, 2 vs. 6 were hospitalised. Three individuals died (all in the placebo group). The majority of the remaining severe cases fulfilled only the oxygen saturation (SpO_2) criterion for severe disease (≤93% on room air).

Updated analyses

The updated efficacy analyses at the end of the double-blind phase (cut-off date 09 July 2021) were performed with additional confirmed COVID-19 cases accrued during blinded, placebo-controlled follow-up, with a median follow-up of 4 months after a single-dose of the COVID-19 Vaccine Janssen.

Table 4: Analysis of vaccine efficacy against symptomatic[a] and severe[b] COVID-19 – 14 days and 28 days after a single-dose

Endpoint[c]	COVID-19 Vaccine Janssen N=19577[d]		Placebo N=19608[d]		% Vaccine Efficacy (95% CI)
	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	
14 days post-vaccination					
Symptomatic COVID-19	484	6685.6	1067	6440.2	56.3 (51.3; 60.9)
18 to 64 years of age	438	5572.0	944	5363.6	55.3 (49.9; 60.2)
65 years and older	46	1113.6	123	1076.6	63.8 (48.9; 74.8)
75 years and older	9	198.2	15	170.9	48.3 (-26.1; 80.1)
Severe COVID-19	56	6774.6	205	6625.2	73.3 (63.9; 80.5)
18 to 64 years of age	46	5653.8	175	5531.4	74.3 (64.2; 81.8)
65 years and older	10	1120.8	30	1093.8	67.5 (31.6; 85.8)
75 years and older	2	199.4	6	172.4	71.2 (-61.2; 97.2)
28 days post-vaccination					
Symptomatic COVID-19	433	6658.4	883	6400.4	52.9 (47.1; 58.1)
18 to 64 years of age	393	5549.9	790	5330.5	52.2 (46.0; 57.8)
65 years and older	40	1108.5	93	1069.9	58.5 (39.3; 72.1)
75 years and older	9	196.0	10	169.3	22.3 (-112.8; 72.1)
Severe COVID-19	46	6733.8	176	6542.1	74.6 (64.7; 82.1)
18 to 64 years of age	38	5619.2	150	5460.5	75.4 (64.7; 83.2)
65 years and older	8	1114.6	26	1081.6	70.1 (32.1; 88.3)
75 years and older	2	197.2	5	170.1	65.5 (-110.7; 96.7)

[a] Symptomatic COVID-19 requiring positive RT-PCR result and at least 1 respiratory sign or symptom or 2 other systemic signs or symptoms, as defined in the protocol.

[b] Final determination of severe COVID-19 cases was made by an independent adjudication committee, who also assigned disease severity according to the definition per FDA guidance.

[c] Co-primary endpoint as defined in the protocol.

[d] Per-protocol efficacy population

Beyond 14 days after vaccination, 18 vs. 74 cases of molecularly confirmed COVID-19 were hospitalised, respectively in the COVID-19 Vaccine Janssen vs. placebo group, resulting in 76.1% (adjusted 95% CI: 56.9; 87.7) vaccine efficacy. A total of 5 cases in the COVID-19 Vaccine Janssen group vs. 17 cases in the placebo group required Intensive Care Unit (ICU) admission and 4 vs.
8 cases in the COVID-19 Vaccine Janssen and placebo group respectively required mechanical ventilation.

Vaccine efficacy against asymptomatic infections at least 28 days after vaccination was 28.9% (95% CI: 20.0; 36.8) and against all SARS-CoV-2 infections was 41.7% (95% CI: 36.3; 46.7).

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants, as well as for participants with and without medical comorbidities associated with high risk of severe COVID-19.

A summary of vaccine efficacy by variant strain is presented in Table 5 below:

Table 5: Summary of vaccine efficacy against symptomatic[a] and severe[b] COVID-19 by variant strain following a single-dose

Variant	Onset	Severity	
		Symptomatic COVID-19 % Vaccine Efficacy (95% CI)	**Severe COVID-19 % Vaccine Efficacy (95% CI)**
Reference	At least 14 days after vaccination	71.5% (57.3; 81.4)	89.7% (57.3; 98.8)
	At least 28 days after vaccination	58.2% (35.0; 73.7)	93.1% (54.4; 99.8)
Alpha (B.1.1.7)	At least 14 days after vaccination	70.1% (35.1; 87.6)	51.1% (-241.2; 95.6)
	At least 28 days after vaccination	70.2% (35.3; 87.6)	51.4% (-239.0; 95.6)
Beta (B.1.351)	At least 14 days after vaccination	38.1% (4.2; 60.4)	70.2% (28.4; 89.2)
	At least 28 days after vaccination	51.9% (19.1; 72.2)	78.4% (34.5; 94.7)
Gamma (P.1)	At least 14 days after vaccination	36.4% (13.9; 53.2)	63.3% (18.3; 85.0)
	At least 28 days after vaccination	36.5% (14.1; 53.3)	63.6% (18.8; 85.1)
	At least 14 days after vaccination	64.8% (47.3; 77.0)	91.1% (38.8; 99.8)

Zeta (P.2)	At least 28 days after vaccination	64.1% (42.5; 78.3)	87.9% (9.4; 99.7)
Mu (B.1.621)	At least 14 days after vaccination	35.8% (1.5; 58.6)	79.4% (38.1; 94.9)
	At least 28 days after vaccination	35.9% (1.7; 58.7)	79.5% (38.5; 94.9)
Lambda (C.37)	At least 14 days after vaccination	10.0% (-39.5; 42.0)	67.4% (-30.6; 94.3)
	At least 28 days after vaccination	10.1% (-39.2; 42.1)	67.6% (-29.8; 94.4)
Delta (B.1.617.2/AY.1/AY.2)	At least 14 days after vaccination	-6.0% (-178.3; 59.2)	NE * NE *
	At least 28 days after vaccination	-5.7% (-177.7; 59.2)	NE* NE*
Other	At least 14 days after vaccination	73.2% (65.4; 79.4)	81.4% (59.8; 92.5)
	At least 28 days after vaccination	69.0% (59.1; 76.8)	75.7% (46.2; 90.3)

[a] Symptomatic COVID-19 requiring positive RT-PCR result and at least 1 respiratory sign or symptom or 2 other systemic signs or symptoms, as defined in the protocol.

[b] Final determination of severe COVID-19 cases was made by an independent adjudication committee, who also assigned disease severity according to the definition per FDA guidance.

* If less than 6 cases are observed for an endpoint then the VE will not be shown. NE = not estimable.

Efficacy of two-doses of COVID-19 Vaccine Janssen administered 2 months apart

A final analysis (cut-off date 25 June 2021) of a multicenter, randomised, double-blind, placebo- controlled Phase 3 study (COV3009) was conducted in North and Latin America, Africa, Europe and Asia to assess the efficacy, safety, and immunogenicity of 2 doses of COVID-19 Vaccine Janssen administered with a 56-day interval. The study excluded individuals with abnormal function of the immune system resulting from a clinical condition, individuals who were under immunosuppressive therapies within 6 months, as well as pregnant women. Participants with stable HIV infection under treatment were not excluded. Licensed vaccines, excluding live vaccines, could be administered more than 14 days before or more than 14 days after the vaccination in the study. Licensed live attenuated vaccines could be administered more than 28 days before or more than 28 days after the vaccination in the study.

A total of 31300 individuals were randomised in the double-blind phase of the study. In total, 14492 (46.3%) individuals were included in the per-protocol efficacy population (7484 individuals received COVID-19 Vaccine Janssen and 7008 individuals received placebo). Participants were followed for a median of 36 days (range: 0-172 days) after vaccination.

Demographic and baseline characteristics were similar among individuals who received at least two doses of the COVID-19 Vaccine Janssen and those who received placebo. In the primary efficacy analysis population, among the individuals who received 2 doses of COVID-19 Vaccine Janssen, the median age was 50.0 years (range: 18 to 99 years); 87.0% (N=6512) of individuals were 18 to 64 years old [with 13.0% (N=972) aged 65 or older and 1.9% (N=144) aged 75 or older]; 45.4% of individuals were female; 37.5% were from North America (United States), 51.0% were from Europe (including UK), 5.4% were from South Africa, 1.9% from Philippines and 4.2% from Latin America. A total of 2747 (36.7%) individuals had at least one pre-existing comorbidity associated with increased risk of progression to severe COVID-19 at baseline. Comorbidities included: obesity defined as BMI ≥ 30 kg/m^2 (24.6%), hypertension (8.9%), sleep apnea (6.7%), type 2 diabetes (5.2%), serious heart conditions (3.6%), asthma (1.7%) and stable/well-controlled HIV infection (1.3%). Other comorbidities were present in ≤ 1% of the individuals.

Vaccine efficacy against symptomatic COVID-19 and severe COVID-19 is presented in Table 6 below:

Table 6: Analysis of vaccine efficacy against symptomatic[a] and severe[b] COVID-19 – 14 days post-booster dose (second dose)

Endpoint	COVID-19 Vaccine Janssen N=7484[c]		Placebo N=7008[c]		% Vaccine Efficacy (95% CI)[d]
	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	
Symptomatic COVID-19	14	1730.0	52	1595.0	75.2 (54.6; 87.3)
Severe COVID-19	0	1730.7	8[e]	1598.9	100 (32.6; 100.0)

[a] Symptomatic COVID-19 requiring positive RT-PCR result and at least 1 respiratory sign or symptom or 2 other systemic signs or symptoms, as defined in the protocol.

[b] Final determination of severe COVID-19 cases was made by an independent adjudication committee, who also assigned disease severity according to the definition per FDA guidance.

[c] Per-protocol efficacy population.

[d] Confidence intervals were adjusted to implement type I error control for multiple testing.

[e] Of the 8 participants with severe disease, 1 was admitted to an intensive care unit.

Final analysis results of variants with sufficient cases available for meaningful interpretations (Alpha [B.1.1.7] and Mu [B.1.621]) show that, after the first dose of COVID-19 Vaccine Janssen, efficacy 14 days post-dose 1 (Day 15-Day 56) for these 2 variants was 73.2% [95% CI: 48.4; 87.1] and 38.6% [95% CI: -43.9; 75.1], respectively. After the second dose (≥71 days), efficacy for Alpha and Mu was 83.7% [95% CI: 43.8; 97.0] and 53.9% [95% CI: -48.0; 87.6], respectively. There were only 7 Delta cases (4 and 3 Delta cases in the COVID-19 Vaccine Janssen group and placebo group, respectively). There were no reference strain cases in either the COVID-19 Vaccine Janssen or placebo group in the follow-up 14 days

after the booster dose (≥71 days).

Vaccine efficacy against asymptomatic infections at least 14 days after second vaccination was 34.2% (95% CI: -6.4; 59.8).

Immunogenicity of a booster dose (second dose) following primary vaccination with COVID-19 Vaccine Janssen

It should be noted that there is no established immune correlate of protection. In a Phase 2 Study (COV2001), individuals 18 through 55 years of age and 65 years and older received a booster dose of the COVID-19 Vaccine Janssen approximately 2 months after the primary vaccination.
Immunogenicity was assessed by measuring neutralising antibodies to SARS-CoV-2 Victoria/1/2020 strain using a qualified wild-type virus neutralisation assay (wtVNA). Immunogenicity data are available from 39 individuals, of whom 15 were 65 years of age and older, and are summarised in Table 7.

Table 7: SARS-CoV-2 Neutralisation Wild Type VNA-VICTORIA/1/2020* (IC50), Study COV2001 Group 1, Per-Protocol Immunogenicity Set**

	Baseline (Day 1)	**28 Days Post-Primary Vaccination (Day 29)**	**Pre-Booster Dose (Day 57)**	**14 Days Post-Booster Dose (Day 71)**	**28 Days Post-Booster Dose (Day 85)**
N	38	39	39	39	38
Geometric mean titre (95% CI)	<LLOQ (<LLOQ, <LLOQ)	260 (196; 346)	212 (142; 314)	514 (357; 740)	424 (301; 597)
Geometric mean fold increase (95% CI) from pre-booster	n/a	n/a	n/a	2.3 (1.7; 3.0)	1.8 (1.4; 2.4)

LLOQ = lower limit of quantification

* Victoria/1/2020 strain is considered as reference strain.

** PPI set: The per-protocol immunogenicity population includes all randomised and vaccinated individuals for whom immunogenicity data are available excluding individuals with major protocol deviations expected to impact the immunogenicity outcomes. In addition, samples obtained after missed vaccinations or individuals with natural SARS- CoV-2 infection occurring after screening (if applicable) were excluded from the analysis.

Neutralising antibody (wtVNA) and S-binding antibody (enzyme-linked immunosorbent assay) increases against the reference SARS-CoV-2 strain were also observed in studies COV1001, COV1002 and COV2001 in a limited number of study participants after a boost given at 2, 3 and
6 months, when compared to pre-boost values. Overall, the increases of geometric mean titres (GMTs) pre-boost to 1 month post-boost ranged from 1.5 to 4.4 fold for neutralising antibodies, and from 2.5 to 5.8 fold for binding antibodies. A 2-fold

decrease in antibody levels was observed 4 months following 2-month booster dose, compared to 1 month following 2-month booster dose. Antibody levels were still higher than antibody levels following a single-dose at a similar timepoint. These data support the administration of a booster dose when administered at an interval of 2 months or longer after primary vaccination.

Immunogenicity of a booster dose following primary vaccination with an approved mRNA COVID-19 vaccine

COV-BOOST study is a multicentre, randomised Phase 2 investigator initiated study (NCT73765130) conducted in the United Kingdom, to evaluate a booster vaccination against COVID 19. Participants were adults aged 30 years or older. A cohort of participants received two doses of Comirnaty (N=89), followed by a booster dose of COVID-19 Vaccine Janssen. The median interval (IQR) was 106 (91- 144) days between the second and booster dose. COVID-19 Vaccine Janssen boosted binding (N=88), pseudovirus neutralising (N=77) and wild type neutralising antibody responses (N=21) against the reference strain, as observed at Day 28. At Day 84 post-boost, GMTs were still higher than pre-boost values. Furthermore, COVID-19 Vaccine Janssen boosted pseudovirus neutralising antibody responses against the Delta variant assessed at Day 28 (N=89).

DMID 21-0012, an independent Phase 1/2 open-label clinical study (NCT04889209) conducted in the United States evaluated a heterologous booster dose of the COVID-19 Vaccine Janssen. Due to the limited sample size, differences observed are only descriptive. A booster dose of COVID-19 Vaccine Janssen was administered to adults who had completed primary vaccination with a Spikevax 2-dose series or a Comirnaty 2-dose series at least 12 weeks prior to enrolment (mean interval [range] of 20 [13-26] and 21 [12-41] weeks for Spikevax and Comirnaty, respectively) and who reported no history of SARS-CoV-2 infection. COVID-19 Vaccine Janssen boosted binding and pseudovirus neutralising antibody responses against the reference strain and the Delta variant in individuals primed with Spikevax 2-dose series (N=49) or Comirnaty 2-dose series (N=50), as observed at Day 15 post-boost. COVID-19 Vaccine Janssen boosted pseudovirus neutralising antibody responses against the Omicron BA.1 variant in individuals primed with Comirnaty 2-dose series (N=50), as observed at Day 29.

Immunogenicity of a booster dose following primary vaccination with an adenoviral vector-based COVID-19 vaccine

COV-BOOST study (see study design above) also evaluated a booster dose of COVID-19 Vaccine Janssen in participants who had received 2 doses of Vaxzevria (N=101). The median interval (IQR) was 77 (72-83) days between the second and booster dose. COVID-19 Vaccine Janssen boosted binding (N=94), pseudovirus neutralising (N=94) and wild type neutralising antibody responses (N=21) against the reference strain. At Day 84 post-boost, GMTs were still higher than pre-boost values. Furthermore, COVID-19 Vaccine Janssen boosted pseudovirus neutralising antibody responses against the Delta variant assessed at Day 28 (N=90).

Descriptive data from the COV-BOOST study and DMID 21-0012 study indicate that boosting with COVID-19 Vaccine Janssen after primary vaccination with an adenoviral vector-based vaccine induces lower antibody responses compared to heterologous boosting with a licensed mRNA vaccine after primary vaccination with an adenoviral vector-based vaccine. The studies also indicate that neutralising antibody titres reached at 1 month post-boost with COVID-19 Vaccine Janssen after

primary vaccination with an mRNA vaccine are comparable to after a homologous boost with an mRNA vaccine.

Immunogenicity of a booster dose following primary vaccination with an inactivated whole-virion COVID-19 vaccine

RHH-001 study is an independent, randomised Phase 4 study (RBR-9nn3scw) conducted at 2 sites in Brazil, to evaluate a booster vaccination against COVID-19 in adults 18 years of age or older. The primary analysis population included participants who had received 2 doses of CoronaVac (N=295) followed by a booster dose of COVID-19 Vaccine Janssen, and were 182 days (plus or minus 30 days) post second dose at the time of boost. Binding antibody titres and neutralising antibody titres, as measured by a pseudovirus and/or wild type virus neutralisation assay, were assessed on Day 28 after the booster dose. COVID-19 Vaccine Janssen boosted binding (N=294) and pseudovirus neutralising antibody responses (N=47) against the reference strain. In a subset of participants (N=20), wild type virus neutralising antibodies were also boosted against the Delta (B.1.617.2) and Omicron (B.1.1.529) variants.

Elderly population

COVID-19 Vaccine Janssen was assessed in individuals 18 years of age and older. The efficacy of COVID-19 Vaccine Janssen was consistent between elderly (≥65 years) and younger individuals (18-64 years).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with COVID-19 Vaccine Janssen 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

Non-clinical data reveal no special hazards for humans based on conventional studies of repeat-dose toxicity and local tolerance, and reproductive and developmental toxicity.

Genotoxicity and carcinogenicity

COVID-19 Vaccine Janssen has not been evaluated for its genotoxic or carcinogenic potential. The components of the vaccine are not expected to have genotoxic or carcinogenic potential.

Reproductive toxicity and fertility

Female reproductive toxicity and fertility were assessed in a combined embryo-foetal and pre- and post-natal development study in the rabbit. In this study a first vaccination of COVID-19 Vaccine Janssen was administered intramuscularly to female rabbits 7 days prior to mating, at a dose equivalent to 2-fold above the recommended human dose, followed by two vaccinations at the same dose during the gestation period (i.e., at gestational days 6 and 20). There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. The parental females as well as their foetuses and offspring exhibited SARS-CoV-2 S protein-specific antibody titers, indicating that maternal antibodies were transferred to the foetuses during gestation. No COVID-19 Vaccine Janssen data are available on vaccine excretion in milk.

In addition, a conventional (repeat-dose) toxicity study in rabbits with COVID-19 Vaccine Janssen did not reveal any effects on male sex organs that would impair male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2-hydroxypropyl-β-cyclodextrin
(HBCD) Citric acid monohydrate
Ethanol
Hydrochloric
acid
Polysorbate-80
Sodium
chloride
Sodium
hydroxide
Trisodium citrate 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

2 years when stored at -25°C to -15°C.

Once removed from the freezer, the unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for a single period of up to 11 months, not exceeding the printed expiry date (EXP).

Once thawed, the vaccine should not be re-

frozen. For special precautions for storage,

see section 6.4.

Opened vial (after first puncture of the vial)

Chemical and physical in-use stability, including during transportation, of the vaccine has been demonstrated for 6 hours at 2°C to 25°C. From a microbiological point of view, the product should preferably be used immediately after first puncture of the vial; however, the product can be stored between 2°C to 8°C for a maximum of 6 hours. The vaccine should be discarded within 6 hours after opening or at the end of the immunization session, whichever comes first. Beyond these times, in-use storage is the responsibility of the user.

6.4 Special precautions for storage

Store and transport frozen at -25°C to -15°C. The expiry date for storage at -25°C to -15°C is printed on the vial and outer carton after “EXP”.

When stored frozen at -25°C to -15°C, the vaccine will be thawed at 2°C to 8°C:

- at 2°C to 8°C: a carton of 10 vials will take approximately 12 hours to thaw, and a single vial will take approximately 2 hours to thaw.

The vaccine can also be stored in a refrigerator or transported at 2°C to 8°C for a single period of up to 11 months, not exceeding the original expiry date (EXP). Upon moving the product to 2°C to 8°C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out. The vaccine can also be transported at 2°C to 8°C as long as the appropriate storage conditions (temperature, time) are applied.

Once thawed, the vaccine cannot be re-frozen.

Keep the vials in the original 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

A 2.5 mL suspension in a multi-dose vial (type I glass) with a rubber stopper (chlorobutyl with fluoropolymer coated surface), aluminium crimp and blue plastic cap. Each vial contains 5 doses of
0.5 mL.

Pack size of 10 multi-dose vials.

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.

- The vaccine comes ready to use once thawed.
- The vaccine is supplied frozen at -25°C to -15°C to countries.
- The vaccine may be supplied frozen at -25°C to -15°C or thawed at 2°C to 8°C for in country distribution.
- Do not re-freeze vaccine once thawed.
- Keep the vials in the original carton in order to protect from light and to record the expiry for the different storage conditions, if applicable.

a. Storage upon receipt of vaccine

IF YOU RECEIVE YOUR VACCINE FROZEN AT -25°C to -15°C you may:

OR

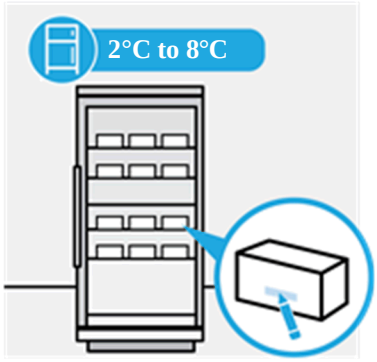
Store in a freezer

- The vaccine can be stored and transported frozen at **-25°C to -15°C**.
- The expiry date for storage is printed on the vial and outer carton after “EXP” (see section 6.4).

Store in a refrigerator

- The vaccine can also be stored and transported at **2°C to 8°C** for a single period of **up to 11 months**, not exceeding the original expiry date (EXP).
- Upon moving the product **to a refrigerator at 2°C to 8°C**, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. **The original expiry date should be crossed out** (see section 6.4).

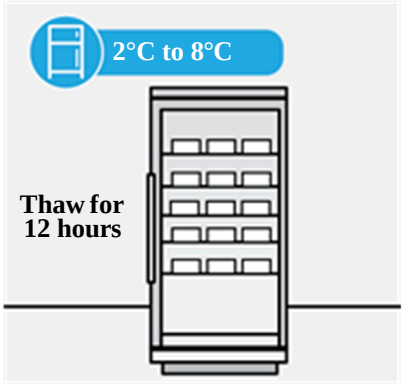
IF YOU RECEIVE YOUR VACCINE THAWED AT 2°C to 8°C (Applicable ONLY to in country distribution) you should store in a refrigerator:



Do not re-freeze if the product is received already thawed at 2°C to 8°C.

Note: If the vaccine is received refrigerated at 2°C to 8°C, check that the expiry date has been updated by the local supplier upon receipt. If you cannot find the new EXP date, contact the local supplier to confirm the refrigerated EXP date. Write the **new expiry date** on the outer carton before the vaccine is stored in the refrigerator. **The original expiry date should be crossed out** (see section 6.4).

b. If stored frozen, thaw vial(s) in a refrigerator before administration



Thaw in refrigerator

- When stored frozen at -25°C to -15°C, a carton of 10 vials will take approximately 12 hours to thaw or individual vials will take approximately 2 hours to thaw **at 2°C to 8°C**.
- If the vaccine is not used immediately, refer to the instructions in section 'Store in a refrigerator'.
- The vial must be kept in the original carton in order to protect from light and to record the expiry for the different storage conditions, if applicable.

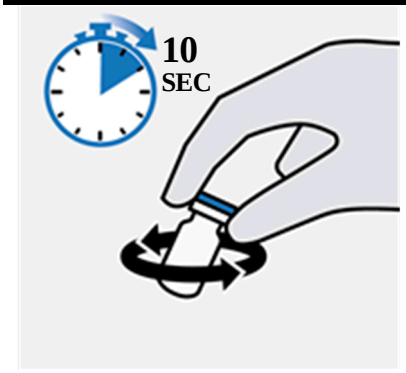
Do not re-freeze once thawed.

c. Inspect vial and vaccine

- COVID-19 Vaccine Janssen is a colorless to slightly yellow, clear to very opalescent suspension (pH 6-6.4).
- The vaccine should be inspected visually for particulate matter and discoloration prior to administration.
- The vial should be inspected visually for cracks or any abnormalities, such as evidence of tampering prior to administration.

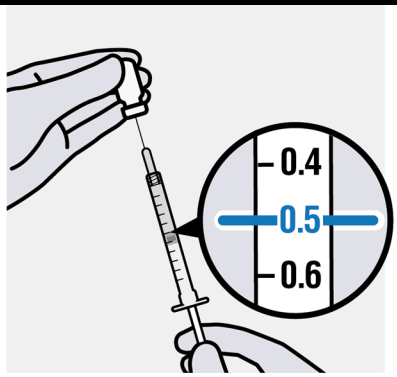
If any of these should exist, do not administer the vaccine.

d. Prepare and administer vaccine



Swirl the vial gently

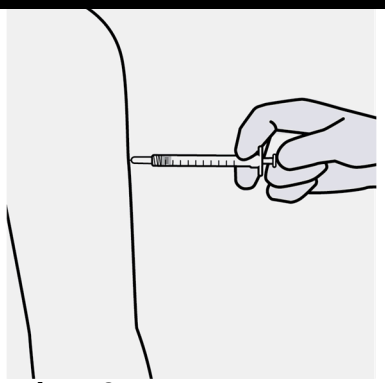
- Before administering a dose of vaccine, swirl the vial gently **in an upright position for 10 seconds**.
- **Do not** shake.



Withdraw 0.5 mL

- Use a sterile needle and sterile syringe to extract a single-dose of **0.5 mL** from the multi-dose vial (see section 4.2).

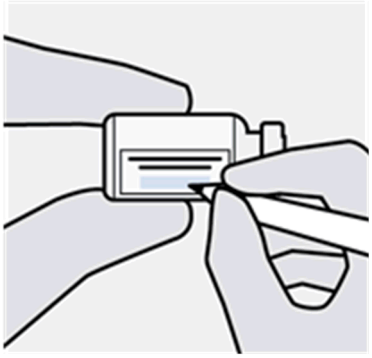
A maximum of 5 doses can be withdrawn from the multi-dose vial. Discard any remaining vaccine in the vial after 5 doses have been extracted.



Inject 0.5 mL

- Administer by **intramuscular injection only** into the deltoid muscle of the upper arm (see section 4.2).

e. Storage after first puncture



Record date and time the vial should be discarded

- After first puncture of the vial record the date and time the vial should be discarded on each vial label.

⚠ Preferably, use immediately after first puncture. After the first puncture of the vial, the vaccine can be held at **2°C to 8°C** for **up to 6 hours**.

- Discard if vaccine is not used within this time.

f. Disposal

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

7. MARKET AUTHORIZATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

8. DATE OF PUBLICATION OR REVISION