

COVID-19 Vaccine Janssen: Contraindication in individuals with previous capillary leak syndrome and update on thrombosis with thrombocytopenia syndrome

Dear Healthcare Professional,

Janssen-Cilag International NV in agreement with the European Medicines Agency and <the National Competent Authority> would like to inform you of the following:

Summary

Capillary leak syndrome (CLS):

- **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 in at least one case.**
- **COVID-19 Vaccine Janssen is now contraindicated in individuals who have previously experienced episodes of CLS.**
- **CLS is 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.**

Thrombosis with thrombocytopenia syndrome (TTS)

- **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.**
- **TTS requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.**

Background on the safety concerns

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

Capillary leak syndrome (CLS)

Very rare cases of capillary leak syndrome (CLS) have been reported following vaccination with COVID-19 Vaccine Janssen, with an estimated reporting rate of one case per approximately 6 million doses. A history of CLS has been reported in at least one of the cases.

CLS is a rare disorder characterised by dysfunctional inflammatory response, endothelial dysfunction, and extravasation of fluid from the vascular space to the interstitial space leading to shock, haemoconcentration, hypoalbuminaemia and potentially consequent organ failure. Patients may present with a rapid swelling of the arms and legs, sudden weight gain and feel faint due to low blood pressure.

Some cases of systemic CLS reported in the literature have been triggered by COVID-19 infection.

CLS occurs rarely in the general population with fewer than 500 cases described worldwide in the literature (National Organisation for Rare Disorders), however, it is likely that estimates are lower than the true event rates.

The European Medicines Agency has recommended an update to the product information of the COVID-19 Vaccine Janssen suspension for injection to reflect the current knowledge of the safety topic.

Thrombosis with thrombocytopenia syndrome (TTS)

A combination of thrombosis and thrombocytopenia (TTS), 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, splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first 3 weeks following vaccination and mostly in women under 60 years of age.

In several of the TTS cases, testing for anti-platelet factor (PF) 4-antibodies was positive or strongly positive. However, the exact pathophysiological mechanism for the occurrence of these thrombotic events is not defined yet, and no specific risk factors have been identified at this stage.

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 skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

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 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.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of COVID-19 Vaccine Janssen in accordance with the national spontaneous reporting system <include the details (e.g., name, postal address, fax number, website address) on how to access the national spontaneous reporting system>.

This product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address (company contact point in the concerned EU MS should be included, respectively)>

Yours Faithfully

Medical Director of Janssen-Cilag International N.V.

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	COVID-19 Vaccine Janssen suspension for injection (Ad26.COVS-S [recombinant])
Marketing authorisation holder(s)	Janssen-Cilag International N.V.
Safety concern and purpose of the communication	Contraindication in individuals with previous capillary leak syndrome (CLS) and update on thrombosis with thrombocytopenia syndrome (TTS) regarding the need to monitor patients with thrombosis OR thrombocytopenia for symptoms of TTS
DHPC recipients	General practitioners, specialists in internal medicine, haematologists, emergency medicine / intensive care specialists, neurologists and vaccination centers. The target group should be further defined at national level, in agreement with the respective national competent authority
Member States where the DHPC will be distributed	All EU member states where COVID-19 Vaccine Janssen is authorised.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	Tue 06 July 2021
DHPC and communication plan (in English) agreed by CHMP	Wed 07 July 2021
Submission of translated DHPCs to the national competent authorities for review	Mon 12 July 2021
Agreement of translations by national competent authorities	Wed 14 July 2021
Dissemination of DHPC	Mon 19 July 2021