VAXZEVRIA/COVID-19 Vaccine AstraZeneca: link between the vaccine and the occurrence of thrombosis in combination with thrombocytopenia

Dear Healthcare Professional,

AstraZeneca AB in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- **A causal relationship between the vaccination with Vaxzevria and the occurrence of thrombosis in combination with thrombocytopenia is considered plausible.**
- **Although such adverse reactions are very rare, they exceeded what would be expected in the general population.**
- **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 and inform vaccinees accordingly.**
- **The use of this vaccine should be in accordance with official national recommendations.**

Background on the safety concern

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.
A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of these cases occurred within the first fourteen days following vaccination and occurred mostly in women under 60 years of age. Some cases had a fatal outcome.
So far, the reported cases occurred after administration of the first dose of Vaxzevria. Experience of exposure to the second dose is still limited.

The PRAC has performed a full investigation including a careful review of EudraVigilance case reports of blood clots and thrombocytopenia in individuals who received the vaccine paying special attention to the information on the sex, age, risk factors, COVID-19 diagnosis (if available), time-to-onset, outcome, and clinical entity. The investigation has also included a related literature review and an observed to expected analysis conducted with EudraVigilance case reports.
Following input from experts, it is considered that an atypical heparin induced thrombocytopenia (aHIT) like disorder is the most plausible hypothesis given the similarities observed in both the

serological profile and clinical presentation of affected patients. It is considered likely that the syndrome, which resembles aHIT, concerns a severe autoantibody against PF4 which exhibits a high binding affinity. It was hypothesised that the antibody itself may change the structure of PF4, similar to what has been shown for aHIT. It was noted that high titres of anti-PF4 antibodies were observed in all patients whose biomaterial was analysed, which contributes to this hypothesis.

A number of studies will be put in place to identify the exact pathophysiological mechanism for the occurrence of these thrombotic events and define the precise magnitude of the risk.

While further evidence is being collected, the PRAC has recommended an update to the product information of Vaxzevria to reflect the current knowledge of the safety issue.
One of these updates is in section 4.8 of the SmPC to reflect thrombocytopenia as an adverse reaction, with a frequency of common, based on data from clinical trials and to include thrombosis in combination with thrombocytopenia with frequency of very rare.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of Vaxzevria 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*>.

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 AstraZeneca AB

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	VAXZEVRIA/COVID-19 Vaccine AstraZeneca suspension for injection (ChAdOx1-S [recombinant])
Marketing authorisation holder(s)	AstraZeneca AB
Safety concern and purpose of the communication	Updated information on the risk of thrombosis in combination with thrombocytopenia.
DHPC recipients	General practitioners, specialists in internal medicine, haematology, emergency medicine and vaccination centres. 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 AstraZeneca is marketed.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	07/04/2021
DHPC and communication plan (in English) agreed by CHMP	08/04/2021
Submission of translated DHPCs to the national competent authorities for review	09/04/2021
Agreement of translations by national competent authorities	12/04/2021
Dissemination of DHPC	13/04/2021