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

Dear Sir or Madam,

In agreement with the European Medicines Agency and the Paul Ehrlich Institute, AstraZeneca GmbH would like to inform you about the following:

Summary

- A causal association between vaccinations with Vaxzevria and the occurrence of thrombosis in combination with thrombocytopenia is considered plausible.
- Although such side effects are very rare, the number exceeded the expected frequency in the general population.
- No specific risk factors have yet been identified.
- Health professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia and inform those vaccinated accordingly.
- The use of this vaccine should be in accordance with the official national vaccination recommendations.

Background on safety concerns

Vaxzevria is indicated for the active immunisation of individuals aged 18 years and older for the prevention of COVID-19 disease caused by SARS-CoV-2.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has very rarely been observed after vaccination with Vaxzevria.
This includes severe cases manifesting as venous thrombosis, including occurrence in unusual areas, such as cerebral sinus vein thrombosis, venous thrombosis in the splanchnic area, and arterial thrombosis, with concomitant thrombocytopenia. Some cases had a fatal outcome. Most of these cases occurred within the first fourteen days of after vaccination and mostly in women under 60 years of age.So far, the reported cases occurred after administration of the first dose of Vaxzevria. The experience after the second dose is still limited.

The PRAC has conducted a comprehensive review, including a thorough review of EudraVigilance case reports of blood clots and thrombocytopenia in people, who received the vaccine, paying particular attention to information on gender, age, risk factors, COVID-19 diagnosis (if available), time to onset and clinical entity were taken into account. The study also included a literature search and an analysis of the observed cases compared to expected cases, based on case reports from the EudraVigilance database.

According to expert information, it can be assumed that one of the atypical heparin-induced thrombocytopenia (aHit) is the most plausible hypothesis, given the similarities in serological profile as well as in the clinical symptoms and course in the affected patients. It is considered likely that the syndrome resembling a Hit is caused by an autoantibody with a high binding affinity to PF4. It is thought that the antibody may alter the structure of PF4, similar to what was shown with aHit. It was also found that high titres were observed in all patients whose

serum was analysed, high titres of anti-PF4 antibodies were observed, strengthening this hypothesis.

A series of studies will be conducted to determine the exact pathophysiological mechanism for the occurrence of this thrombosis events, and to define the exact extent of the risk.

While further data are being collected, the PRAC has recommended an update to the product information of Vaxzevria to reflect current knowledge on this aspect of safety. One of these updates relates to section 4.8 of the SmPC, thrombocytopenia has been identified as an adverse reaction with a frequency of common, based on data from clinical trials. Furthermore, thrombosis in combination with thrombocytopenia has been added with a frequency of very rare.