



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use
EMA/H/A-5(3)/1507

Interim Opinion of the Committee for Medicinal products for Human Use pursuant to Article 5(3) of Regulation (EC) No 726/2004 for

Vaxzevria

Basis for the interim opinion

On 9 April 2021, the European Commission presented to EMA a request under Article 5(3) of Regulation (EC) No 726/2004 for the Agency, on behalf of the Commission, to carry out as a matter of great urgency a further analysis and stratification of data on risk of thrombosis in combination with thrombocytopenia (TTS) in the context of the benefits of Vaxzevria, in different age groups and/or sex as well as possible other risk factors that could be identified. Moreover, the Agency was asked to provide, if possible, a recommendation on the administration of the second dose of Vaxzevria on the basis of the available data. The notification of this request is appended to this interim opinion.

The procedure started on 14 April 2021.

Interim Opinion

The CHMP, having considered the matter as set out in the appended assessment report, based on the available data and the discussion within the Committee, is of the opinion that:

In relation to the further analysis and stratification of data:

- Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The overall benefits of Vaxzevria in the prevention of COVID-19 outweigh risks from adverse events including thrombosis in combination with thrombocytopenia (TTS).
- The favourable effects of vaccination with Vaxzevria have been demonstrated in clinical trials. Vaccination has benefits in protecting against COVID-19 and observational studies suggest that it reduces the risk of hospitalisation from COVID-19.
- Vaxzevria has been associated with an increased risk of TTS. The frequency of those events has been characterised as very rare based on current reporting rates. No risk factors have been identified for TTS at present.



- To support decision making relating to vaccination campaigns at national level, the reports of TTS are presented in the context of the benefits of vaccination stratified by age and considering the background infection rate. The analysis does not take into consideration individual risk of infection, e.g. occupation or risk of severe COVID-19 based on comorbidities. When conducting this analysis, the benefits of the vaccine were described using data from the marketing authorisation dossier of Vaxzevria, published studies, data provided by the Member States and ECDC and were estimated in terms of:
 - COVID-19 related hospitalisations prevented
 - COVID-19 related ICU admissions prevented
 - COVID-19 related deaths prevented
- In this analysis, it was not possible to further stratify risk by sex, as data on sex was received from only a subset of Member States and it was not possible to validate extrapolation to the remaining Member States.
- Benefits were expressed as a function of age and level of viral circulation. The risk of TTS was estimated based on a number of spontaneously reported cases in EudraVigilance in patients having received Vaxzevria and the exposure data for Vaxzevria.
- In order to reflect the different situations in the different MSs and changing situation over time and understanding that different parameters may be important for decision making, different scenarios have been assessed, which gave different estimates of benefits and risks. Infection rate and hospitalisation, ICU and death are used to contextualise the occurrence of TTS.
- Different assumptions on estimates on the level of benefit and level of risk have been made:
 - several assumptions on the level and duration of protection provided by the vaccine;
 - two assumptions for risk using the absolute number of cases of TTS reported to EudraVigilance and adjusting this number based on presumed underreporting.
- In addition, the circulation of the virus differs in both temporal and geographical terms in Europe. As Member States only reported data from 2021 onwards, the COVID-19 incidence rate for the low exposure scenario (virus circulation in September 2020) was calculated based on the case-based data from the ECDC (drawn from 9 Member States).
- This exercise has put the very rare cases of TTS in the context of the benefits of vaccination. The analyses conducted show that the benefits of vaccination increase with increasing age and increasing infections rates. Details on different scenarios of age and infection rate for hospitalisation, ICU admission and death, together with TTS risk are presented in the assessment report based on different assumptions of vaccine effectiveness and risk.
- These are only interim results and may be subject to change as more is known about the risk of TTS and the favourable effects of vaccination with Vaxzevria. However, these results based on the agreed methodology can be used to help guide the vaccination decisions at national level including on optimal use of Vaxzevria as part of the armamentarium.
- To better support this contextualisation exercise, key aspects of this analysis have been presented graphically.

In relation to the administration of the second dose of Vaxzevria:

- The CHMP considered the alternative scenarios of administering Vaxzevria with an interval longer than the recommended 4-12 weeks, of not administering a second dose at all or administering an mRNA vaccine as second dose.
- The CHMP concluded that two separate doses of Vaxzevria should be administered 4 to 12 weeks apart, in line with the current product information. The mechanism behind the observed cases of TTS is unclear, and there has not been enough exposure and follow-up time to determine whether the risk of TTS with a second dose will differ from that of the first dose.
- For subjects that will not receive a second dose of Vaxzevria, at present there are no or limited data on alternatives for the administration of a second dose of Vaxzevria.

Finally, it is highlighted that this is an interim opinion based on currently available data and CHMP will, continue to consider these aspects as new information becomes available and issue a final conclusion in due time.

The Icelandic and the Norwegian CHMP member(s) agree(s) with the above-mentioned recommendation of the CHMP.

This interim opinion is forwarded to the European Commission, to Member States, to Iceland and Norway, together with its appendixes.

This interim opinion is without prejudice to the outcome of the ongoing review under Article 5(3) of Regulation (EC) No 726/2004.

The CHMP conclusions will be published on the EMA website.