

## Summary of MHRA's regulatory position for Acute Disseminated Encephalo-Myelitis (ADEM) reported following COVID-19 Vaccines

### Background

The MHRA is the regulator of medicines, medical devices and blood components for transfusion in the UK. The Agency rigorously uses science and data to inform decisions, enable medical innovation and to make sure that medicines and healthcare products available in the UK are safe and effective.

The MHRA's responsibilities are to:

- ensure medicines, medical devices and blood components for transfusion meet applicable standards of safety, quality and efficacy (effectiveness)
- secure safe supply chain for medicines, medical devices and blood components
- promote international standardisation and harmonisation to assure the effectiveness and safety of biological medicines
- educate the public and healthcare professionals about the risks and benefits of medicines, medical devices and blood components, leading to safer and more effective use
- enable innovation and research and development that is beneficial to public health
- collaborate with partners in the UK and internationally to support our mission to enable the earliest access to safe medicines and medical devices and to protect public health<sup>1</sup>

Part of the MHRA's monitoring role includes reviewing reports of suspected side effects – known as suspected Adverse Drug Reactions (“ADRs”) – through the Yellow Card scheme<sup>2</sup>. The MHRA operates the Yellow Card scheme on behalf of the Commission on Human Medicines (CHM). The scheme collects and monitors information on suspected safety concerns or incidents involving vaccines, medicines, medical devices, and e-cigarettes. The scheme relies on voluntary reporting of suspected adverse incidents by healthcare professionals and members of the public (patients, users, or carers). The purpose of the scheme is to provide an early warning that the safety of a product may require further investigation.

Yellow Card reports of ADRs are evaluated, together with additional sources of evidence, by a team of safety experts to identify any new safety issues or side effects. The MHRA applies statistical techniques that can tell us whether we are seeing more events than we would expect to see, based on what is known about background rates of illness in the absence of vaccination, if this information is available. This aims to allow for factors such as coincidental illness. Spontaneous reporting systems like the Yellow Card system are subject to both over- and under-reporting; the MHRA uses awareness campaigns and user-friendly reporting methods to encourage reporting.

---

<sup>1</sup> <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/about>

<sup>2</sup> <https://yellowcard.mhra.gov.uk/information>

The MHRA supplements this form of safety monitoring with other epidemiology studies, including analysis of data on national vaccine usage; anonymised GP-based electronic healthcare records; company data and other healthcare data. The MHRA also takes into account international experience based on data from other countries using the same vaccines. Further information is available in the COVID-19 vaccine surveillance strategy published on the MHRA's website<sup>3</sup>.

### **Acute Disseminated Encephalo-Myelitis (ADEM)**

ADEM is classically described as a uniphasic syndrome of brain inflammation and demyelination, occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. The diagnostic hallmark of ADEM is the demonstration of scattered, focal or multifocal (disseminated) areas of inflammation and demyelination within cerebral subcortical and deep cortical white matter; while grey matter involvement may be seen as well (particularly in the thalamus), this is generally a minor component compared with white matter disease.<sup>4</sup>

ADEM has been identified following vaccination, notably with vaccines for smallpox and rabies, but vaccine-associated ADEM is considered rare and accounts for less than 5% of all ADEM cases<sup>5</sup>. ADEM is an Adverse Event of Special Interest (AESI) for the COVID-19 vaccines. AESIs are pre-specified side effects which were highlighted for close monitoring prior to deployment of the COVID-19 vaccines<sup>6</sup>.

### **Pre-authorisation data**

ADEM was not reported in clinical trials for the AstraZeneca or mRNA COVID-19 vaccines.

### **Post-authorisation data**

The COVID-19 vaccine marketing authorisation holders were all required to submit monthly safety updates to the MHRA following deployment of their products. From assessment of the reports submitted by AstraZeneca in early 2021 the MHRA considered that the available data did not support a signal for ADEM or encephalitis at that time. ADEM continued to be closely monitored in company periodic reports, with the MHRA concluding no need for regulatory action due to insufficient evidence of a causal association with vaccination.

In June 2022 the MHRA became aware that the Australian authority had received a fatal report of ADEM following the AstraZeneca vaccine and was exploring the addition of ADEM to the product information<sup>7</sup>.

The MHRA presented a review of ADEM following the AstraZeneca vaccine to the Commission on Human Medicines' (CHM) COVID-19 Vaccine Benefit Risk Expert Working Group (EWG) in August 2022. The data sources used included results from clinical trials, published literature articles, Yellow Card reports and observed/expected analyses of Yellow Cards. The EWG considered that the data supporting a causal association were limited and did not recommend regulatory action, however, the Group recommended that the MHRA

---

<sup>3</sup> <https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance>

<sup>4</sup> <https://www.sciencedirect.com/science/article/pii/S0264410X07004975?via%3Dihub>

<sup>5</sup> <https://www.sciencedirect.com/science/article/pii/S0264410X19300751>

<sup>6</sup> <https://speacsafety.net/tools/aesi-lists/>

<sup>7</sup> <https://www.tga.gov.au/news/covid-19-vaccine-safety-reports/covid-19-vaccine-weekly-safety-report-16-06-2022#vaxzevria-astrazeneca-vaccine>

work with the UK Health Security Agency (UKHSA) to explore the feasibility of conducting an observational study to further characterize the risk.

In May 2023 the MHRA presented an update of the previous safety review to the EWG, including results of an epidemiological study<sup>8</sup> and from observed/expected analyses conducted by UKHSA using secondary user services data. These results indicated that there was a statistically significantly increased risk of ADEM following dose 1 of the AstraZeneca vaccine in both analyses; no signals were identified for either of the mRNA vaccines. The EWG were informed that the Australian authority had added ADEM as a warning to the AstraZeneca vaccine product information. The EWG concluded that a precautionary approach should be pursued and regulatory updates to the product information should be considered to reflect the potential risk of ADEM; this was approved by the CHM.

### **Regulatory action taken by MHRA**

In November 2023 the GB product information for the AstraZeneca vaccine<sup>9</sup> was updated to include a warning for ADEM (information added to section 4.4, Special Warnings and Precautions for Use, of the Summary of Product Characteristics and section 2, what you need to know before you are given Vaxzevria/Warnings and Precautions, of the Patient Information Leaflet). The event is described as 'extremely rare'. As of 11 June 2024, the MHRA's Yellow Card database<sup>10</sup> shows a total of 20 reports with the preferred term of 'acute disseminated encephalomyelitis' for the AstraZeneca vaccine,

## **MHRA**

**August 2024**

---

<sup>8</sup> <https://www.tandfonline.com/doi/full/10.1080/21645515.2024.2311969>

<sup>9</sup> <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca>

<sup>10</sup> <https://yellowcard.mhra.gov.uk/idaps/CHADOX1%20NCOV-19>