

Summary of MHRA’s regulatory position for specified events reported with COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and COVID-19 Vaccine Moderna

Issue

The MHRA has been requested by the NHS Business Services Authority to provide an update on the current regulatory position regarding COVID-19 vaccination and:

- Guillain Barre syndrome and the Pfizer BioNTech and Moderna COVID-19 vaccines
- De-myelinating conditions (other than Guillain-Barre Syndrome (GBS))

Summary of current MHRA position

The following summaries concern the COVID-19 vaccines previously or currently widely used in the UK vaccination programme.

Official vaccination data from the UK Public Health agencies are no longer routinely published for all UK nations. Therefore, data for first and second doses will not be reported beyond 11 September 2022 as regional data is no longer available. Data on the third doses and any booster doses will continue to be updated. From 23 November 2022 vaccine usage will be derived from individual nations’ data projected according to the UK population estimates published by the Office for National Statistics (ONS)¹.

Vaccine Brand	Dose 1*	Dose 2*	Dose 3/Booster**
Pfizer/BioNTech Monovalent	27,208,588	25,021,273	32,467,667
Pfizer/BioNTech Bivalent	N/A	N/A	9,657,858
Moderna Monovalent	1,707,521	1,573,656	13,143,677
Moderna Bivalent	N/A	N/A	8,933,613
AstraZeneca	24,896,911	24,167,711	59,743

*Up to DLP 11/09/2022

** Up to DLP 23/11/2022

Guillain Barre syndrome

Guillain-Barré syndrome (GBS) is an Adverse Event of Special Interest for all COVID-19 Vaccines. GBS is currently not recognised as an undesirable effect of COVID-19 vaccine Pfizer/BioNTech and COVID-19 Vaccine Moderna. Up to and including the 23 November 2022, the MHRA has received 116 suspected reports of GBS following use of the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech. For the monovalent and bivalent COVID-19 Vaccine Moderna there have been 31 reports of GBS. A review of GBS with COVID-19 Vaccine Pfizer/BioNTech and COVID-19 Vaccine Moderna was undertaken by the MHRA in July 2021 and presented to the COVID-19 vaccine Expert Working Group for consideration. At the time of this review the available spontaneous reporting data and epidemiological analyses did not suggest an association between GBS and the COVID-19 vaccine Pfizer/BioNTech. The data at the time of this review also did not suggest a signal regarding

¹ <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting>

GBS with the Moderna vaccine. The MHRA continues to monitor suspected reports of GBS and related conditions.

Demyelinating conditions (other than GBS)

De-myelinating conditions included within this summary are the PTs recognised under the MedDRA HLGTT ‘Demyelinating disorders’:

18q minus syndrome, Acute disseminated encephalomyelitis, Acute haemorrhagic leukoencephalitis, Adrenoleukodystrophy, Aicardi-Goutieres syndrome, Alexander disease, Autoimmune demyelinating disease, Band sensation, CADASIL, CARASIL syndrome, Canavan disease, Cerebrohepatorenal syndrome, Clinically isolated syndrome, Concentric sclerosis, Delayed myelination, Demyelination, Dysmyelination, Encephalitis periaxialis diffusa, Intramyelinic oedema, Ischaemic demyelination, Krabbe's disease, Leukodystrophy, Leukoencephalomyelitis, Marburg's variant multiple sclerosis, Metachromatic leukodystrophy, Multiple sclerosis, Multiple sclerosis pseudo relapse, Multiple sclerosis relapse, Myelin oligodendrocyte glycoprotein antibody-associated disease, Neuromyelitis optica pseudo relapse, Neuromyelitis optica spectrum disorder, Niemann-Pick disease, Osmotic demyelination syndrome, Pelizaeus-Merzbacher disease, Primary progressive multiple sclerosis, Progressive multifocal leukoencephalopathy, Progressive multiple sclerosis, Progressive relapsing multiple sclerosis, Radiologically isolated syndrome, Refsum's disease, Relapsing multiple sclerosis, Relapsing-remitting multiple sclerosis, Secondary progressive multiple sclerosis, Tumefactive multiple sclerosis, Uhthoff's phenomenon.

Demyelinating disorders are conditions that impacts the nervous system in which the myelin sheath of neurons is damaged. This damage impairs the conduction of signals in the affected nerves causing deficiency in sensation, movement, cognition or other nerve function. Demyelinating disorders can be genetic, but also have been associated to occur post infection, from autoimmune reactions or following environmental exposure to noxious chemicals. Symptoms and signs will differ between specific demyelinating disease, but common manifestations include ataxia, clonus, dysarthria, paraesthesia, impaired coordination, muscular weakness and other neurological symptoms. Diagnosis can involve various techniques where exclusion of other conditions that have overlapping symptoms is a primary focus and often utilises MRI, CSF analysis and FLAIR alongside clarifying diagnostic criteria.

Demyelinating disorders are considered as AESIs for all vaccines within the UK.

COVID-19 Vaccine Pfizer/BioNTech (monovalent and bivalent preparation)

(Reaction) PT	(Reaction) ADR number (n)
Multiple sclerosis	43
Multiple sclerosis relapse	28
Demyelination	13
Acute disseminated encephalomyelitis	9
Neuromyelitis optica spectrum disorder	2
Relapsing-remitting multiple sclerosis	2
Band sensation	1
Clinically isolated syndrome	1
Tumefactive multiple sclerosis	1

Demyelinating disorders are not currently recognised as undesirable effects for COVID-19 vaccine Pfizer/BioNTech. Up to and including the DLP 02/12/2022, the Agency has received 93 reports (constituting 100 events) that detail a PT event that falls under the HLT 'Demyelinating disorders'. The most commonly reported events are 'Multiple sclerosis' with 43 reports, 'Multiple sclerosis relapse' with 28 reports, 'Demyelination' with 13 reports and 'Acute disseminated encephalomyelitis' with 9 reports.

Multiple sclerosis (MS), relapse of MS, relapsing-remitting MS, neuromyelitis optica spectrum disorder (NMOSD) and acute disseminated encephalomyelitis (ADEM) have previously been considered by the Agency and taken for advice to the Expert Working Group (EWG) as part of separate papers that consider wider topics. The first paper from May 2021 reviewed neurological disorders and included MS and NMOSD within the review. The EWG considered Yellow Card data, company data and observed versus expected epidemiological analysis and agreed that the evidence for MS and NMOSD did not suggest a causal association between these events and COVID-19 vaccine Pfizer/BioNTech and regulatory action was not felt to be warranted.

The second paper that looked at autoimmune conditions and associated flare ups following vaccination which further reviewed MS in June 2022 similarly concluded that there was no clear indication of a signal based on limited reporting following review of Yellow Card data, clinical trial data, company data, literature and international regulatory experience.

A separate paper reviewing the risk of ADEM with the AstraZeneca vaccine was presented to the EWG in August 2022 and included consideration of data for ADEM with Pfizer/BioNTech and Moderna. The EWG supported the Agency position that there was limited evidence available from the Yellow Card data, company data, PRAC assessment of the PSUR and O/E analysis, to support a causal indication for the vaccine-event combination of ADEM and AZ, and no immediate regulatory action was warranted. However, it is important to note that due to the biological plausibility of this event, further studies are being investigated by the MHRA into the association of COVID-19 vaccine AstraZeneca and ADEM. As part of this work, wider considerations to other encephalopathies and possible differential diagnoses including NMOSD and anti-myelin oligodendrocyte glycoprotein (MOG) are being given alongside further comparison of this wider scope for both COVID-19 Pfizer/BioNTech vaccine and COVID-19 vaccine Moderna.

Demyelinating disorders of this nature are under review by the Agency however the current evidence does not suggest a causative link with COVID-19 vaccine Pfizer/BioNTech.

COVID-19 Vaccine Moderna (monovalent and bivalent preparations)

(Reaction) PT	(Reaction) ADR number (n)
Multiple sclerosis relapse	11
Multiple sclerosis	6
Demyelination	2
Multiple sclerosis pseudo relapse	1
Progressive multiple sclerosis	1
Uhthoff's phenomenon	1
Band sensation	1

Demyelinating disorders are not currently recognised as undesirable effects for COVID-19 vaccine Moderna. Up to and including the DLP 02/12/2022, the Agency has received 20 reports (constituting 23 events) that detail a PT event that falls under the HLT 'Demyelinating disorders'. The most

commonly reported events are 'Multiple sclerosis' with 11 reports, 'Multiple sclerosis relapse' with 6 reports and 'Demyelination' with 2 reports.

As described for Pfizer/BioNTech, consideration has been given to MS, NMSOD and ADEM in reviews presented to EWG with respect to Moderna COVID-19 vaccine as the suspect vaccine. Similarly, the currently available evidence did not indicate strong evidence of a causal association of these events with the COVID-19 Vaccine Moderna.

Demyelinating disorders of this nature are under continuous review by the Agency with COVID-19 Vaccine Moderna.

COVID-19 Vaccine AstraZeneca

(Reaction) PT	(Reaction) ADR number (n)
Multiple sclerosis	80
Multiple sclerosis relapse	68
Demyelination	31
Acute disseminated encephalomyelitis	17
Band sensation	7
Neuromyelitis optica spectrum disorder	6
Myelin oligodendrocyte glycoprotein antibody-associated disease	4
Clinically isolated syndrome	3
Multiple sclerosis pseudo relapse	2
Uhthoff's phenomenon	2
Autoimmune demyelinating disease	1
Progressive multiple sclerosis	1
Relapsing multiple sclerosis	1
Relapsing-remitting multiple sclerosis	1
Tumefactive multiple sclerosis	1

Demyelinating disorders are not currently recognised as undesirable effects for COVID-19 vaccine AstraZeneca. Up to and including the DLP 02/12/2022, the Agency has received 216 reports (constituting 225 events) that detail a PT event that falls under the HLT 'Demyelinating disorders'. The most commonly reported events are 'Multiple sclerosis' with 80 reports, 'Multiple sclerosis relapse' with 68 reports, 'Demyelination' with 31 reports, ADEM with 17 reports, 'Band sensation' with 7 reports, NMOSD with 6 reports and MOG with 4 reports.

As described for Pfizer/BioNTech and Moderna vaccines, consideration has been given to MS, NMSOD and ADEM in reviews presented to EWG with respect to AstraZeneca COVID-19 vaccine as the suspect vaccine. Similarly, for MS and NMSOD, the currently available evidence did not indicate strong evidence of a causal association of these events with the COVID-19 Vaccine AstraZeneca.

As noted for Pfizer/BioNTech, a review of the risk of ADEM with COVID-19 Vaccine AstraZeneca was taken for advice to the EWG in August 2022. This review was conducted following notification of a fatal report from the TGA of AZ vaccine with ADEM, prompting subsequent review of the Yellow Card data and other available evidence. At the time of this review, 16 UK reports had been received however the limited clinical detail presented within the spontaneous reports meant meaningful assessment against the complex causality/diagnostic criteria was difficult. Literature, company data, PRAC assessment of this topic within the MAH PSUR and internal observed versus expected analysis was also considered. The EWG endorsed the Agency conclusion that no immediate regulatory action

was warranted, however further characterisation of the risk would be useful given biological plausibility of this event in conjunction with the current listing of Guillain-Barre Syndrome and transverse myelitis.

Demyelinating disorders of this nature, including ADEM and wider encephalopathies as described above, are under continuous review by the Agency with COVID-19 Vaccine AstraZeneca.

December 2022

Review of regulatory summary

The regulatory position for GBS has not changed.

The regulatory position for ADEM, one of the demyelinating disorders describe above, has changed since the original summary was created. ADEM is now included as a warning in the product information for the AstraZeneca COVID-19 vaccine. For details see the regulatory summary prepared separately on ADEM.

MHRA

12 August 2024