To: SofS

From: Dr Sarah Branch, Interim Director, VRMM Division, MHRA
Cleared Dr June Raine, CEO MHRA
Date: 7 April 2021
Copy: PS/ Minister Dorries

ASTRAZENECA COVID-19 VACCINE SAFETY REPORTS: ADVICE OF COMMISSION ON HUMAN MEDICINES

Issue	The MHRA has concluded its initial investigation into reported cases of serious adverse events, specifically blood clots (thromboses) with low platelet count, suspected to be associated with the AZ vaccine. The CHM met in extraordinary session on 4 April to consider more recently available UK data and analyses, and then on 6 April to consider additional analysis from AZ. This submission outlines their advice and MHRA action in the light of this.
Timing	Urgent: there are planned public communications for the afternoon of 7 April.
Recommendation	Ministers are advised that MHRA intends to update UK information for healthcare professionals and vaccine recipients, in line with CHM advice, and is preparing to communicate that publically on 7 April. Work to establish an international consensus position is ongoing.

Introduction

1. The MHRA updated Ministers on 18 and 27 March, and on 2 April on the concerns about serious adverse events - the combination of a rare form of thrombosis in the brain (cerebral sinus vein thrombosis, CSVT) or other venous thromboses with thrombocytopenia (reduced blood platelets) temporally associated with vaccination with the AstraZeneca COVID-19 vaccine.

2. The previous submissions updated Ministers as follows:

    - Analysis of data with a data lock of 24 March was presented to EWG on 25 March and CHM on 27 March. At that point, there were 30 cases, with 7 deaths, and no regulatory action was proposed, but CHM recommended there should be clear public communications, so that there was clear and transparent communication about the investigation into the possible association with the vaccine, while being clear that the events were rare and that the benefit/risk of the vaccine remained positive. These figures were accordingly published with some explanation as part of the weekly ADR (adverse events report) on Thursday 1 April. The submission of 27 March refers.

    - A further tranche of data, with a data lock of 29 March was presented to EWG on 31 March and to CHM on 1 April – on that date, the cumulative total was 62 cases, including 17 deaths. The CHM advised that an update to healthcare and vaccine recipient, information and public communications, was now appropriate; the

submission of 2 April recommended that these be prepared as part of a co-ordinated cross-system communications effort, originally planned for Tuesday 6 April.

Update on adverse events data

3. MHRA has continued to receive and analyse reports of these adverse events. The CHM considered the latest data, and additional information from PHE on the benefits of Covid-19 vaccination, at an extra-ordinary meeting on 4 April and advised MHRA on actions to consider, and discuss with the company. We were advised later that day that AZ had produced a new global data set, which the company wished to be considered, before the MHRA took action, following CHM recommendations. EWG and CHM therefore convened on 6 April 2021 to do so. The CHM has now provided advice as detailed in this submission.

4. The current position is as follows:

   - Up to and including 31 March, of 91 relevant adverse event reports received, MHRA scientific assessors considered there to be 79 cases "confirmed, probable or possible"; and of these, 19 people have now died. 20.2 million doses of the COVID-19 Vaccine AstraZeneca had been administered up to and including 31 March. These cases all relate to first doses and there have been no reported cases from a second dose of the vaccine. There are still relatively few second doses administered.

   - While there are reports of co-morbidities or underlying conditions for some of those affected, it is not clear what, if any, these play in posing clinical risk. There are a number of cases where there is no previous related medical history. Fatality rates are relatively high, at around 25% of reported events.

   - The numbers of events remain small in comparison to the number of doses of the vaccine administered, with an overall incidence of about 4 per million, with a higher risk in younger age groups. The totality of the data reviewed indicates that there may be a higher risk in younger age groups than older ones, noting that there may be under-reporting of incidents in older age groups who received the AZ vaccine first in the UK.

CHM advice and AZ discussion: 4 April

5. The CHM considered the latest case information (as at 31 March) at an extraordinary meeting on 4 April 2021. They advised that the benefit/risk analysis remained positive for above age 40 but that the AZ vaccine should not be issued to those under 40; that pregnant women, who were particularly at risk of blood clots, should not be offered the AZ vaccine; that people with known thromboembolic events with thrombocytopaenia should not be given the AZ vaccine; and that the MHRA Clinical Trials Unit should hold urgent discussions with those conducting the clinical trial on the use of the AZ vaccine in children.

6. Following the CHM meeting, there was a meeting with AZ, to explain the CHM recommendations and to seek their view, in line with usual practice. While our earlier information from the company had been that they too were looking to put in place an age restriction, they informed us in the evening of 4 April that they had further considered a larger, new global data set of their own, and concluded that no age restrictions could be justified, taking into account this wider evidence base. This was relevant information, and AstraZeneca were invited to present these data to the Expert

Working Group of CHM on Tuesday 6 April, to explain their position. This again is in line with usual practice although, given the situation, on an expedited timeframe.

AZ presentation and CHM advice: 6 April

7. Astra Zeneca provided their analysis to MHRA late on 5 April and then presented this to EWG on 6 April; CHM considered the same information. The company analysis considered 184 cases, all but two from the UK and Europe, and analysed these against assumptions of likely mortality from Covid-19 and expected background rates of the cases of concern, using a US database. Astra Zeneca concluded that the benefit/risk remained positive for the vaccine, in all age ranges because the current evidence made it difficult to identify a particular age cut-off and that no causal link had been established. However, they acknowledged that their analysis showed that the rates of thromboembolic events and CVST, combined with thrombocytopenia, were observed more than expected in age groups up to 49 (Europe) and 39 (UK). The company also informed EWG that the trial sponsor had halted recruitment into, and vaccinations of children, in the clinical trial of the use of the vaccine in children. They were keen to emphasise their willingness to work further with MHRA and other regulatory authorities.

8. The EWG and CHM thoroughly considered the analysis. They concluded that the information presented on mortality prevented was likely to over-estimate the benefit, as it was based on mortality data for the full pandemic rather than (as with PHE analysis) looking at the impact of likely future waves, in the context of some population vaccination. They also questioned the use of the US database to estimate background rates of the incidence of the events in question, as this was drawn from insurance company records and would therefore only cover the subset of the population with insurance, and likely act to exclude some vulnerable groups. The CHM considered that the evidence further strengthened the likelihood of an association, but did recognise it was possible to consider there to be a continuum ranging from higher risk in younger age groups to less risk in older age groups, and, at this point, it was hard to conclude on a clear “cut off” age in terms of benefit/risk analysis.

CHM advice

9. In the light of the discussion with AZ, the CHM re-considered their conclusions of 4 April, and have given the following advice:

    - The further cases and consistency of the pattern strengthens the evidence of an association with the AZ vaccine. EWG and CHM members are in consensus that there is an association with the AZ vaccine, but that a causal link has not yet been established.

    - The product and patient information should be updated to state the risks of these events, but not to give a specific “cut-off” age at which the benefit/risk analysis was negative. This was to recognise that the numbers are small, conclusions may change as more data comes in, and that it was valid to consider that there was a continuum, rather than a specific age – making it inappropriate at this stage to issue a clear restriction in the regulatory authorisation – which tended to carry significant weight, and was difficult to alter. The CHM did consider that the JCVI should consider deployment strategies for different ages, in the light of the data and analysis currently available. The CHM noted that this was the approach taken in other countries where it was the JCVI equivalents, which had taken deployment decisions, rather than the national regulators putting in place regulatory restriction.

This global discussion will be beneficial in balancing the situation in countries with access to developed health systems, differing mortality rates from Covid-19, and access to alternative vaccines, with those countries with limited resources and access to vaccines through AZ's role in the COVAX facility. Local benefit-risk decisions may be more appropriate depending on the epidemiology of the disease in different age-groups in different countries.

Next steps

15. The MHRA is now agreeing updates to the patient and product information with AZ in line with the CHM advice. These updates state the risk of these possible side effects, and provide additional guidance for health care professionals. This would include: a description of these adverse events, the symptoms that healthcare professionals and patients should look out for; the need for prompt and appropriate treatment; and information about the people with pre-existing conditions predisposed to thrombosis who should not receive the vaccine. The MHRA had shared previous versions with AZ, since last Thursday following the CHM meeting on that day and anticipate reaching agreement today. The MHRA is able to change these documents without company agreement, if that becomes necessary.

Communications – cleared by Rachel Bosworth

16. As outlined above, clear and co-ordinated public communications, and advice to healthcare professionals, is essential to inform the public and retain confidence in the vaccination programme. There continues to be extensive media interest in the numbers of cases and fatalities, and our last published case numbers were the 30 cases and 7 fatalities, to the 24 March data lock point, published as part of the MHRA weekly ADR report on Thursday 1 April. There is clearly a risk that the numbers published so far are considerably lower than those cases considered by CHM on 4 April, and we anticipate that the regular Thursday ADR report publication will be of continued interest to journalists.

17. MHRA Communications have worked with DHSC Communications, NHSE/I and PHE on the cross-system communications approach, messaging and timing. This is currently planned for the afternoon of Wednesday 7 April, with a joint media briefing from MHRA and JCVI, media statements, publication of updated information for the public and health professionals, and other supporting materials. This approach has been shared with No 10. We are currently expecting EMA communications on the same afternoon, but this may be brought forward.

Legal – cleared by Name Redacted

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