Medicines & Healthcare products
Regulatory Agency

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United Kingdom
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[redacted]

09 October 2023

Dear [redacted]

Thank you for your request for information dated 11 September 2023, we have provided our answers beneath each of your questions, as listed below.

1. **What ongoing investigations regarding mechanism of reaction for tinnitus and Vaxzevria vaccine are being conducted?**

Our response:
The MHRA is not undertaking such investigations and therefore we do not hold the information that you have requested.

2. **Can you provide me with the number of adverse events the Yellow Card system holds for the Vaxzevria vaccine by Batch number? How many vaccine doses are in a batch?**

Our response:
Please find table 1 below for the number of UK spontaneous suspected Adverse Drug Reaction (ADR) reports for the COVID-19 AstraZeneca (Vaxzevria) vaccine by batch number up to and including 22/09/2023. We have provided you with the 10 batches associated with the highest number of reports, due to the large number of unique batches that were extracted within our database. Please note batch number is not a mandatory field and is not always provided. Additionally, batch is a free text field and as such some reports may not have been included where the number was incorrectly provided.

Table 1 - Total number of spontaneous UK Yellow Card adverse drug reaction (ADR) reports of the top 10 most reported batch numbers for the COVID-19 AstraZeneca vaccine up to and including 22/09/2023

Count	Batch number	Number of ADR reports
1	4120Z003	7509
2	PV46664	6648
3	PV46671	5534
4	AB0012	4978
5	PV46672	4777
6	PW40009	4456
7	PV46669	4133
8	PV46673	4071
9	PV46663	3936
10	AB0011	3921

Please note, not all batches of the COVID-19 vaccines are the same size and some batches may have had more wastage than other batches or be distributed more widely outside of the UK. Therefore, we would not expect the number of ADR reports for all batches to be the same as they have been administered to different numbers of patients.

Furthermore, different batches would have been used at different stages of the vaccination campaign, and in different patient groups, which could also impact reporting rates. For example, reporting rates were typically higher at the beginning of the vaccination campaign as individuals received their first dose and the likelihood of experiencing a reaction, as well as the propensity to report it, differs across patients of different ages. Please note that our analysis of these reports, which takes into account product batch number, did not result in any safety concerns, and therefore the provided data cannot be used to infer any safety concerns. Please be assured that the MHRA reviews this data regularly and we would communicate any concerns raised with the public and healthcare professionals. If you would like further information on batch usage, please contact the UK Health Security Agency (UKHSA) who hold this information.

When considering the attached spontaneous ADR data, it is important to be additionally aware of the following points:

- A reported reaction **does not** necessarily mean it has been caused by the vaccine, only that the reporter had a suspicion it may have. The fact that symptoms occur after use of a vaccine, and are reported via the Yellow Card Scheme, does not in itself mean that they are proven to have been caused by the vaccine. Underlying or concurrent illnesses may be responsible and such events can also be coincidental.

- It is also important to note that the number of reports received via the Yellow Card scheme does not directly equate to the number of people who suffer adverse reactions and therefore cannot be used to determine the incidence of a reaction. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, the extent of use of a particular drug, and may be stimulated by promotion and publicity about a drug.

Regarding the second part of your question, on average there are one million doses in a batch. Some earlier batches had half a million doses.

3. **Where there any changes to the manufacturing process for the Vaxzevria vaccine between the product used in the clinical trials and the product used in the UK vaccination programme? If so, was batch PV46672 manufactured pre or post those change and during the rollout or at any point throughout the early part of 2021?**

Our response:
Batch PV46672 was made using the commercial manufacturing process (i.e. Process 4). Some changes were made between the different process versions, as is expected during the development of any product before commercialisation.

4. **Can you explain what changed in linking tinnitus to the Vaxzevria vaccine between April 2022 when the Benefit Risk Expert Working Group saw no signals in the data and April 2023 when the MHRA amended the Product Characteristics of Vaxzevria? Particuly given vaccination with Vaxzevria had all but been stopped in early 2022, what new data had come to light?**

Our response:
The COVID-19 vaccines used in the primary UK vaccination programme, including Vaxzevria, were approved following a rigorous review by the MHRA and the Government's independent advisory body, the Commission on Human Medicines (CHM), of their safety, quality and effectiveness. The MHRA concluded that the COVID-19 vaccines were safe and effective and that the benefits outweigh any known risk.

No medicine or vaccine is completely risk-free and hence the MHRA continually monitored the safety of the COVID 19 vaccines through a comprehensive COVID-19 Vaccine Surveillance Strategy. This monitoring strategy was proactive and based on a wide range of information sources, with a dedicated team of scientists continually reviewing information to look for safety issues or any unexpected, rare events.
We also worked closely with our international counterparts to gather information on the safety of vaccines in other countries.

As with all vaccines and medicines, the safety of COVID-19 vaccines was continuously monitored and if a new safety issue be confirmed we took action to promptly inform patients and healthcare professionals and took appropriate steps to mitigate any identified risk and protect public health.

In the case of tinnitus in association with Vaxzevria (COVID-19 vaccine AstraZeneca), in September 2021 the CHM COVID-19 Vaccines Benefit Risk Expert Working Group reviewed the evidence available at the time regarding deafness and tinnitus in association with the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines. As you are aware, the Expert Working Group concluded that the available data at the time did not support an association between any of the three COVID-19 vaccines being used in the UK and hearing impairment however this issue should remain under ongoing review by the MHRA.

In July 2022, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) advised that tinnitus would be added to the European Union (EU) product information for Vaxzevria as a side effect of Vaxzevria. The PRAC recommendation was based on spontaneous reports of cases of tinnitus reported with the use of Vaxzevria and new data on tinnitus provided from an ongoing clinical trial with the vaccine.

Following the update to the EU product information, in November 2022 the CHM COVID-19 Vaccines Benefit Risk Expert Working Group further considered the additional and cumulative evidence now available regarding tinnitus and COVID-19 vaccines. The Expert Working Group considered that the imbalance of cases of tinnitus in the newly available clinical trial data for COVID-19 vaccine AstraZeneca, (with more events of tinnitus in participants who received COVID-19 vaccine AstraZeneca than in those who received placebo) provided some evidence of an association between Vaxzevria and tinnitus. The Expert Working Group agreed that the GB Vaxzevria product information should be updated to include tinnitus as an undesirable effect.

Subsequently, in January 2023, the GB Summary of Product Characteristics and patient information leaflet for Vaxzevria were updated to add tinnitus as an uncommon side effect.

5. Where is the documentation regarding the original Vaxzevria phase 1, 2 and 3 trial data, particularly relating to the adverse event data?

Our response:
The UK public assessment report is available, in which there is a table of contents to locate information related to clinical data, which includes adverse event data:
a185f6cb8cd8e195ed877311fc7e8d39375d5f37 (windows.net)

The clinical aspects of this product are also discussed in the EPAR below, the introduction to the section begins 'Clinical aspects' page 54/181. Reference is made to adverse events throughout this section, but there is also a discussion on clinical safety on page 138.
vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf (europa.eu)

In addition, the EMA have a publication scheme which discusses the clinical data which they publish.
publication scheme

Home - Clinical Data Publication - clinicaldata.ema.europa.eu

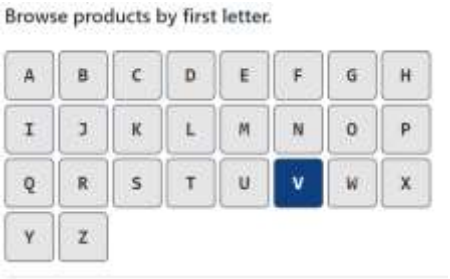
To visit the EMA repository online please follow the link above, on the right hand side of the page will be some text instructing new users to create an account, see screenshot below). Once an account is created the product can be searched and the clinical data can be scrolled through using the arrow keys on the keyboard to navigate.

1.

2.

Select ‘Browse search’.

3.



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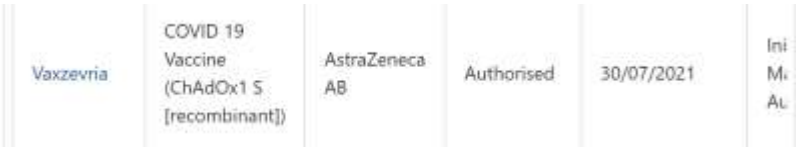

Select the relevant product name, and check the procedure type, the main submission is the ‘initial marketing authorisation’ (not fully shown in screenshot above).

6. Can you provide access to the ISS, Integrated Summary of Safety that would be in the regulatory submission?

Our response:
The ISS, Integrated Summary of Safety, appears to be a document used to support FDA (US) medicine applications, therefore, this document is not held.

The closest equivalent document in the UK and EU is likely to be the clinical overview. This document is present on the EMA clinical data repository (described above). The clinical overview will be updated when new clinical data are submitted or further analyses conducted.

If you disagree with how we have interpreted the Freedom of Information Act 2000 in answering your request, you can ask for an internal review. Please reply to this email, within two months of this reply, specifying that you would like an Internal Review to be carried out. Please remember to quote the reference number above in any future communications.

If you were to remain dissatisfied with the outcome of the internal review, you would have the right to apply directly to the Information Commissioner for a decision. Please bear in mind that the Information Commissioner will not normally review our handling of your request unless you have first contacted us to conduct an internal review.

The Information Commissioner can be contacted online via an electronic form:
https://ico.org.uk/make-a-complaint/foi-and-eir-complaints/foi-and-eir-complaints/

Or

by writing to:
Information Commissioner's Office
Wycliffe House
Water Lane
Wilmslow
Cheshire
SK9 5AF
Yours sincerely
MHRA Customer Service Centre
Medicines and Healthcare products Regulatory Agency
10 South Colonnade, Canary Wharf, London E14 4PU

Yours sincerely,

FOI Team