,

Thank you for your inquiry regarding AZD1222. The following information is being provided, as a professional courtesy, in response to your request:

AstraZeneca COVID-19 Vaccine (ChAdOx1 S [recombinant])-Thromboembolic Events

The enclosed information may include information that is not found in the currently approved labeling information for AZD1222. The information is intended to provide pertinent data in response to your
request and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by Health Canada and as described in the labeling information.

AstraZeneca COVID-19 Vaccine Product Monograph Information

AstraZeneca COVID-19 Vaccine (COVID-19 Vaccine (ChAdOx1-S [recombinant])) is indicated for active immunization of individuals 18 years of age and over for the prevention of coronavirus disease 2019 (COVID-19).

You can access additional information regarding the AstraZeneca COVID-19 vaccine at: www.azcovid-19.com.

You can access the COVAX label for COVID-19 Vaccine AstraZeneca at: http://www.covax.azcovid-19.com/

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We have saved your name and contact information in our database in accordance with Canadian Privacy Legislation for follow-up purposes only. Please contact us if you wish to have your information removed from our electronic record.

Thank you for your interest in AZD1222. In order to monitor the safety of AZD1222, we encourage clinicians to report suspected adverse events to AstraZeneca. To report an adverse event or if we may be of further assistance, such as additional information or translation of this response, please contact AstraZeneca at
1-800-668-6000 (press option 3) or visit http://contactazmedical.astrazeneca.com.

Sincerely,

Virginia Gribaudo-Bartocci
Medical Information Specialist – ERP

INQ 05940789

AstraZeneca COVID-19 Vaccine (ChAdOx1 S [Recombinant]) – Thromboembolic Events

AstraZeneca is providing you with this material as an information service and professional courtesy. Providing this information does not constitute any recommendation for use.

The WHO, ISTH, EMA, and MHRA have all stated the benefits of vaccination with ChAdOx1 S (recombinant) continue to outweigh the risks.[1,2,4,9]

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Summary

- AstraZeneca COVID-19 Vaccine (manufactured by AstraZeneca) and COVISHIELD (manufactured by Serum Institute of India) are ChAdOx1-S recombinant vaccines developed by AstraZeneca and the University of Oxford. Health Canada has reviewed the manufacturing information for these vaccines and found them to be comparable.
- Reviews by the EMA, MHRA and WHO have determined a possible link between the occurrence of specific thrombosis/thrombotic events with thrombocytopenia (e.g., CSVT) and AstraZeneca COVID-19 Vaccine.[4,9,10]
  - A causal link has not yet been confirmed, warranting further investigation
- AstraZeneca is actively working to understand the individual cases, epidemiology, and potential mechanism to explain these rare events.[5]
- A possible explanation is an immune response leading to a heparin-induced thrombocytopenia (HIT) like disorder.[4]
- In clinical trials, thromboembolic events were balanced between participants receiving AstraZeneca COVID-19 Vaccine and control.[7,11,12]
- Healthcare professionals should instruct vaccinated individuals to seek immediate medical attention if they develop signs/symptoms of thromboembolism or thrombocytopenia.[4,6]

Product Monograph Information[3]

INDICATIONS

AstraZeneca COVID-19 Vaccine (COVID-19 Vaccine (ChAdOx1-S [recombinant])) is indicated for active immunization of individuals 18 years of age and over for the prevention of coronavirus disease 2019 (COVID-19).

For more therapeutic and safety information, please refer to the AstraZeneca COVID-19 Vaccine Product Monograph available at: www.astrazeneca.ca

Background

- Approximately 34 million people have received the ChAdOx1 S (recombinant) vaccine in the European Economic Area and UK as of April 4, 2021.[4]
- An EU drug safety database (EudraVigilance) search as of April 4, 2021, has identified 169 cases of cerebral venous sinus thrombosis (CVST) thrombotic cases and 53 cases of splanchnic (abdominal) vein thrombosis.[4]
- AstraZeneca is actively working with regulators and to understand the individual cases, epidemiology, and potential mechanism to explain these rare events.[5]

- Health care professionals should be aware of the signs/symptoms of thromboembolism or thrombocytopenia and instruct individuals to seek immediate medical attention if they develop any of the following symptoms following vaccination:[4,6]
    - Shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision and/or tiny blood spots under the skin beyond the injection site.

Real-World Evidence

European Medicines Agency (EMA) Review

- Following reports of thromboembolic events in mid-March 2021, the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA conducted a review of a signal of blood clots in people vaccinated with ChAdOx1 S (recombinant). The PRAC involved experts in blood disorders in its review and worked closely with other health authorities, including the MHRA.[7]
- 62 cases of CVST and 24 cases of splanchnic vein thrombosis were reviewed as of March 22, 2021, with 18 cases reported fatal.[4]
- On April 7, 2021, PRAC concluded that unusual blood clots with low blood platelets should be listed as a very rare side effect for ChAdOx1 S (recombinant).[4]
    - A possible explanation for these events is an immune response leading to a HIT-like disorder.[4]
    - Most of the cases reported have occurred in women under 60 years of age and within 2 weeks of vaccination.
    - However, specific risk factors have not been identified, based on current evidence.
- The EMA maintains the benefits of the vaccine continue to outweigh the risk of side effects.[4]

The Medicines and Healthcare Products Regulatory Agency (MHRA) Review

- The MHRA also conducted a rigorous scientific review, of all available data, including a detailed review of reported cases and data from hospital admissions and general practitioner records, confirmed by the government's independent advisory group, the Commission on Human Medicines.[8]
- The review evaluated 79 cases (44 cases of CVST and 35 reports of other thrombosis events with low platelets) out of 20.2 million doses given in the UK, as of March 31, 2021.[9]
    - All 79 cases occurred after a first dose of the vaccine, with 19 cases reported as fatal
- Following the review, the MHRA concluded a possible link between these rare blood clots and ChAdOx1 S (recombinant), requiring further investigation.[9]
- The MHRA maintains the benefits of the vaccine continue to outweigh the risk of side effects with careful consideration to individuals at higher risk for these rare blood clots.[9]

WHO Review[10]

- Based on the current evidence, a causal relationship between ChAdOx1 S (recombinant) and the occurrence of blood clots with low platelets is plausible but not confirmed.
    - Further investigation is required to determine this relationship and potential risk factors.
- These events are considered very rare amongst the 200 million individuals who have received ChAdOx1 S (recombinant).

Clinical Trials

US Phase III Trial (D8110C00001)[11]

- The US Phase III trial showed that ChAdOx1 S (recombinant) was well-tolerated with no safety concerns identified.
- A specific review of thrombotic events and CVST found no increased risk of thrombosis or events characterized by thrombosis among the 21,583 participants receiving at least one dose of the vaccine.

COV001/COV002/COV003/COV005 Pooled Study[12,13]

- The overall safety of ChAdOx1 S (recombinant) is based on an interim pooled data analysis from four clinical trials conducted in the UK (COV001, COV002), Brazil (COV003) and South Africa (COV005).
- Across the four studies, SAEs (n=175) occurred in 168 participants, with 84 events occurring in the ChAdOx1 S (recombinant) group and 91 in the control group.
- Thrombotic, thromboembolic, and neurovascular events are monitored as adverse events of special interest (AESI)
- Please refer to the table below for additional information:

Table 1: AESIs (Thrombotic Events)[13]

Thrombotic Event Type	ChAdOx 1 S (Recombinant) (N=12,021)	Control (N=11,724)
Coronary artery occlusion	1 (<0.1%)	1 (<0.1%)
Deep vein thrombosis	0	1 (<0.1%)
Ischemic stroke	1 (<0.1%)	0
Pulmonary embolism	1 (<0.1%)	0
Thrombosis	1 (<0.1%)	0
Thrombophlebitis	0	1 (<0.1%)
Transient ischemic attack	0	2 (<0.1%)

Reporting of Post-marketing Adverse Events

- It is AstraZeneca policy to provide adverse event information to health care professionals from the labeling information, the published literature, and clinical trial data for our marketed products.
  - Key findings from the clinical trials, including safety information, form the basis for the labeling information.
- We generally do not provide specific AE information from the AstraZeneca Safety database because of the inherent limitations of spontaneous reports.
  - Such limitations include but are not limited to adverse event recognition, underreporting, reporting biases, estimates of patient exposure, report quality, and lack of established causality of reported adverse events.
- The safety profile of each AstraZeneca product is continuously monitored, and the labeling information is updated whenever new safety issues are identified.

Abbreviations:
AESI: adverse events of special interest; **CVST**: cerebral venous sinus thrombosis; **EU**: European Union; **EMA**: European Medicines Agency; **HIT**: heparin-induced thrombocytopenia; **MHRA**: Medicines and Healthcare products Regulatory Agency; **ISTH**: The International Society on Thrombosis and Haemostasis; **PRAC**: Pharmacovigilance Risk Assessment Committee; **UK**: United Kingdom; **WHO**: The World Health Organization.

Adverse Event Reporting

Key clinical findings from clinical trials, including safety information form the basis for the Product Monograph. Our AstraZeneca Safety database includes data from Clinical Trials and post-marketing reports. These reports are monitored, and the Product Monograph is updated when new safety issues are established.

In order to monitor the safety of our products we encourage clinicians to report suspected adverse events to AstraZeneca at 1-800-433-0733 or by submitting an electronic report using the following link: https://contactazmedical.astrazeneca.com/content/astrazeneca-champion/ca/en/amp-form.html

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