Important Safety Information on the Importation of AstraZeneca COVID-19 Vaccine with English-only Vial and Carton Labels (US-Labelled Supply)

2021/03/31

IMPORTANT: **Access to Canadian-specific labelling information during the initial distribution of the AstraZeneca COVID-19 Vaccine (US-labelled vaccine supplies).**

Audience
Healthcare professionals including infectious disease physicians, pharmacists, family physicians, public health officials, nurses and nurse practitioners, and healthcare professionals at identified points of use.

AstraZeneca Canada Inc. (AstraZeneca) (the Canadian importer and distributor) is initially distributing AstraZeneca COVID-19 Vaccine doses directly to locations where administration of the vaccine will occur, as outlined by provincial and territorial governments and public health authorities.

Key messages

- **Further to the February 26, 2021 authorization of the AstraZeneca COVID-19 Vaccine in accordance with the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, AstraZeneca is providing US-labelled vaccine supplies with English-only vial and carton labels (see Appendix A) in order to expedite the distribution of AstraZeneca COVID-19 Vaccine in Canada.**
- **AstraZeneca COVID-19 Vaccine with US labels is the same as the Health Canada authorized AstraZeneca COVID-19 Vaccine in all aspects (i.e., formulation, strength, route of administration).**
- **Healthcare professionals are advised that:**
  - **Important Canadian-specific information is absent from the US vial and carton labels (see the Information for healthcare professionals section).**
  - **The expiration date is not printed on the US vial and carton labels. Healthcare professionals must verify the expiration date prior to vaccination. The expiration date for the corresponding batches/lots can be found in the 'Products affected' section of this document, by going to www.AZCOVID-19.com website, or by scanning the QR code on the US English-only carton label.**

- **The Canadian Product Monograph, which is available in French and English on Health Canada's Drug Product Database, the federal government's covid-vaccine.canada.ca website, and at www.AZCOVID-19.com, should be referenced for complete product information.**
- **The Canadian-specific labelling information in French and English can be accessed at www.AZCOVID-19.com, or by scanning the QR code on the US English-only carton label. This information is also available on the federal government's covid-vaccine.canada.ca website.**
- **AstraZeneca has developed Health Canada approved vial and carton labels in French and English (see Appendix B), and has made them available on the www.AZCOVID-19.com website. The labels are also available on the federal government's covid-vaccine.canada.ca website.**
- **Paper copies of the Canadian Product Monograph, including the Patient Medication information, in French and English will be made available at the points of use for healthcare professionals and patients.**
- **Paper copies of the Health Canada approved vial and carton labels in French and English will also be made available (see Appendix B) for reference by healthcare professionals at the points of use.**
- **On February 26, 2021, Health Canada also permitted the use of AstraZeneca COVID-19 Vaccine, COVAX English-only vials and carton labels.**

What is the issue?

AstraZeneca COVID-19 Vaccine was authorized for use in accordance with the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19. As an extraordinary measure to provide earlier access to vaccine supplies in Canada in the context of the global pandemic, AstraZeneca is providing the vaccine with US vial and carton labels. These labels are presented in English-only and are missing some important Canadian-specific information normally found on Health Canada approved labels (see the Information for healthcare professionals section).

Products affected

Product Name	Dosage Form, Strength, and Route of Administration	Country of Origin and Identifying Code	Manufacturer	Importer and Supplier in Canada
AstraZeneca COVID-19 Vaccine, (ChAdOx1-S [recombinant])	Suspension for Intramuscular Injection 10 Multi-dose vials (each vial contains 10 doses of 0.5 mL)	USA NDC 0310-1222-10 (vial) NDC 0310-1222-15 (carton)	AstraZeneca Pharmaceuticals LP	AstraZeneca Canada Inc.

Expiration date information for the US-labelled batches/lots	
Batch Number	**Expiry Date**
MT0055	31-May-2021
MT0056	31-May-2021
NA0079	30-Jun-2021

Background information

AstraZeneca COVID-19 Vaccine is indicated for active immunization of individuals 18 years of age and older for the prevention of coronavirus disease 2019 (COVID-19).

Given the public health emergency resulting from the current pandemic, Health Canada has authorized the importation, sale, and advertising of US-labelled AstraZeneca COVID-19 Vaccine with vial and carton labels that are in English-only for the initial distribution of the vaccine. This allows earlier access to the vaccine for the Canadian population ahead of the Canadian-labelled AstraZeneca COVID-19 Vaccine being available, and facilitates the global deployment of this vaccine across many countries given the high demand.

AstraZeneca COVID-19 Vaccine with US English-only labels is the same as the Health Canada authorized AstraZeneca COVID-19 Vaccine in all aspects (i.e., formulation, strength, route of administration) and should be used in Canada for the same indication and per the same vaccination schedule.

Information for healthcare professionals

In order to provide rapid access to AstraZeneca COVID-19 Vaccine for Canadians, AstraZeneca will provide US-labelled vaccine supplies with vials and cartons labelled in English-only for a limited time period.

Healthcare professionals are advised that:

- The approved Canadian Product Monograph, which is available in French and English on Health Canada's Drug Product Database, the federal government's covid-vaccine.canada.ca website or at www.AZCOVID-19.com, should be

used for complete product information.

- The following important Canadian-specific information is absent from the US vial and carton labels:
    - Drug Identification Number (DIN)
    - name and address of the Canadian DIN holder
    - name and address of the Canadian importer and distributor
    - all corresponding text in French
    - expiry date

- The expiration date is not printed on the vial and carton labels. Healthcare professionals must verify the expiration date prior to vaccination. The expiration date for the corresponding batches/lots can be found in the 'Products affected' section of this document, by going to www.AZCOVID-19.com website, or by scanning the QR code on the US English-only carton label.
- The vial and/or carton labels for the initial supplies of vaccines may include the text "Emergency Use Authorization", reference to the FDA-authorized fact sheet, and National Drug Code number, "NDC 0310-1222-10" (vial) and "NDC 0310-1222-15" (carton).This should be disregarded as this is not relevant to the Canadian authorization.
- The Canadian-specific labelling information, in French and English, can be accessed at www.AZCOVID-19.com, or by scanning the QR code on the US English-only carton label. This information is also available on the federal government's covid-vaccine.canada.ca website.
- Paper copies of the Canadian Product Monograph, including the Patient Medication Information, in French and English will be made available at the points of use for this vaccine.
- AstraZeneca has developed French and English vial and carton labels that Health Canada has approved (see Appendix B), and has made them available on the www.AZCOVID-19.com website for reference by healthcare professionals. The labels are also available on the federal government's covid-vaccine.canada.ca website.
- Paper copies of the Health Canada approved vial and carton labels in French and English will also be made available (see Appendix B), for reference by healthcare professionals at the points of use.
- On February 26, 2021, Health Canada also permitted the use of AstraZeneca COVID-19 Vaccine, COVAX English-only vials and carton labels.
- For any product or general inquiries, contact AstraZeneca Medical Information at 1-800-668-6000, or email medinfo.canada@astrazeneca.com.

Action taken by Health Canada

On September 16, 2020, Canada's Minister of Health approved an Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 to expedite the authorization for the importation, sale, and advertising of

drugs used in relation to COVID-19 while taking into consideration urgent public health needs. The Interim Order will expire after one year. Health Canada authorized the use of AstraZeneca COVID-19 Vaccine under the Interim Order on February 26, 2021, and this vaccine has been added to the "List of authorized drugs, vaccines and expanded indications" for COVID-19.

Health Canada is permitting the use of US English-only labels for a limited period. Health Canada also permitted the use of COVAX English-only vials and carton labels.

Health Canada has imposed terms and conditions requiring AstraZeneca to provide vaccine supplies with Canadian-specific labels as soon as possible. Vaccines with Canadian-specific labelling information will be implemented by June 2021. Health Canada has made full labelling information available in French and English on the federal government's covid-vaccine.canada.ca website.

Health Canada has worked with AstraZeneca to prepare this alert for the AstraZeneca COVID-19 Vaccine and is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system, as well as through social media channels, including LinkedIn and Twitter.

Report health or safety concerns

Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any serious or unexpected side effects in patients receiving AstraZeneca COVID-19 Vaccine should be reported to your local Health Unit or AstraZeneca.

AstraZeneca Canada Inc.
1004 Middlegate Road, Suite 5000
Mississauga
Ontario L4Y 1M4

For any medical questions related to AstraZeneca COVID-19 Vaccine, contact Medical Information at 1-800-668-6000) or submit a form online at www.azcovid-19.com.

If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit. Alternatively, you can report adverse events to AstraZeneca online at https://contactazmedical.astrazeneca.com.

For other health product inquiries related to this communication, contact Health Canada at:

Biologic and Radiopharmaceutical Drugs Directorate
E-mail: hc.brdd.dgo.enquiries.sc@canada.ca

Original signed by

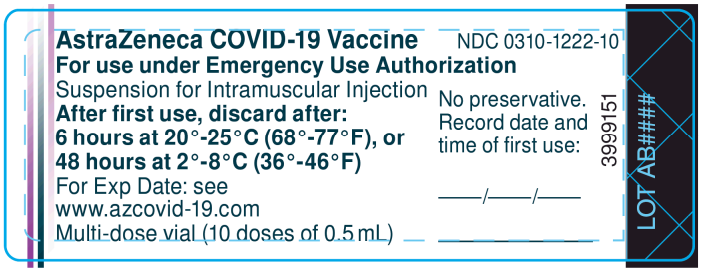
Dr. Neil Maresky, M.B., B.Ch.
Vice President, Scientific Affairs

- Appendix A: Vial and carton labels for 5 mL AstraZeneca COVID-19 Vaccine with English-only labelling (US-labelled supply)
- Appendix B: Vial and carton labels for 5 mL AstraZeneca COVID-19 Vaccine with Health Canada approved English and French labelling (Canadian-labelled supply)

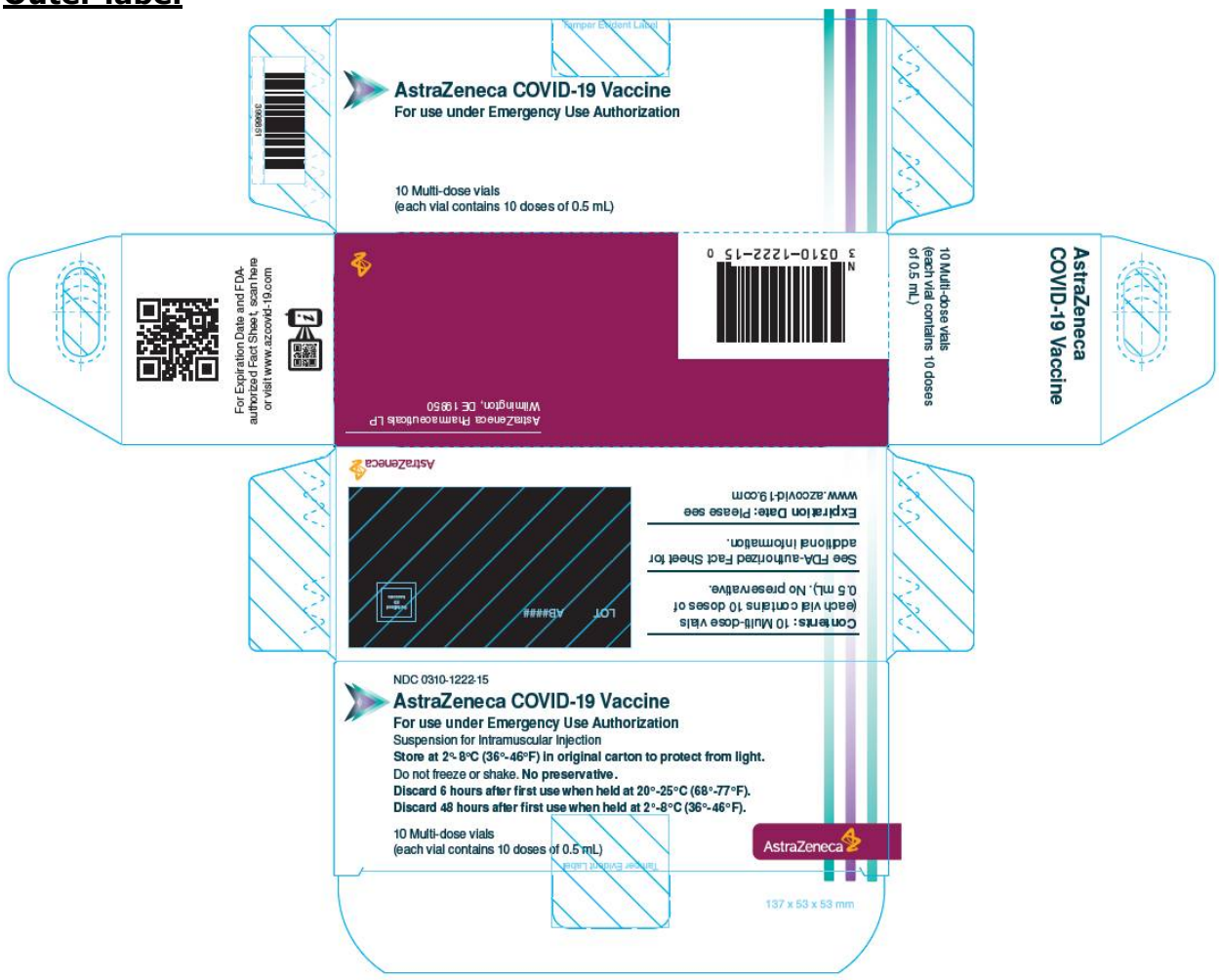
Appendix A: Vial and carton labels for AstraZeneca COVID-19 Vaccine with English-only labelling (US-labelled supply)

US supply (5 mL – 10 doses)

Inner label



Outer label



US supply (5 mL – 10 doses)

Inner label
AstraZeneca COVID-19 Vaccine NDC 0310-1222-10
For use under Emergency Use Authorization
Suspension for Intramuscular Injection
After first use, discard after:
6 hours at 20°-25°C (68°-77°F), or
48 hours at 2°-8°C (36°-46°F)
For Exp Date: see www.azcovid-19.com
Multi-dose vial (10 doses of 0.5mL)
3999151
No preservative.
Record date and time of first use:
———/———/———
——————————

Outer label
NDC 0310-1222-15
AstraZeneca COVID-19 Vaccine
For use under Emergency Use Authorization
Suspension for Intramuscular Injection
Store at 2°-8°C (36°-46°F) in original carton to protect from light.
Do not freeze or shake. No preservative.
Discard 6 hours after first use when held at 20°-25°C (68°-77°F).
Discard 48 hours after first use when held at 2°-8°C (36°-46°F).
10 Multi-dose vials (each vial contains 10 doses of 0.5 mL)

For Expiration Date and FDA authorized Fact Sheet, scan here or visit www.azcovid-19.com

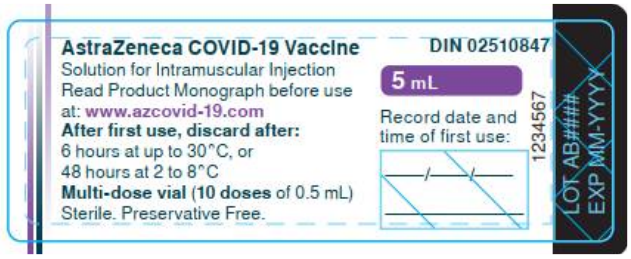
Contents: 10 Multi-dose vials (each vial contains 10 doses of 0.5 mL). No preservative.
See FDA-authorized Fact Sheet for additional information.
Expiration Date: Please see www.azcovid-19.com

AstraZeneca Pharmaceuticals LP Wilmington, DE 19850

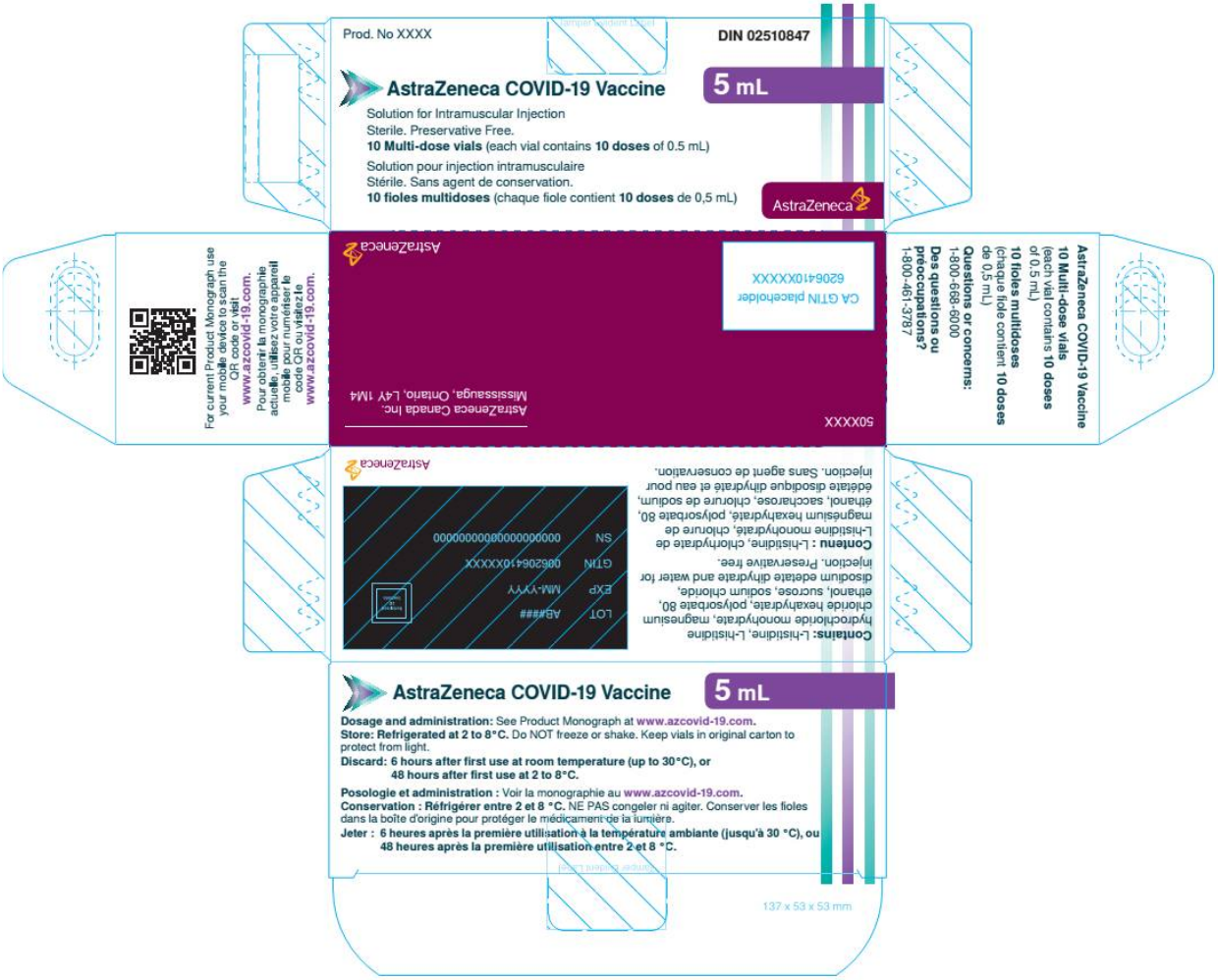
Appendix B: Vial and carton labels for AstraZeneca COVID-19 Vaccine with Health Canada approved English and French labelling (Canadian-labelled supply)

CANADIAN supply (5 mL – 10 doses)

Inner label



Outer label



CANADIAN supply (5 mL – 10 doses)

Inner label
AstraZeneca COVID-19 Vaccine
DIN 02510847
Solution for Intramuscular Injection 5 mL
Read Product Monograph before use
at: www.azcovid-19.com
After first use, discard after:
6 hours at up to 30°C, or
48 hours at 2 to 8°C
Multi-dose vial (10 doses of 0.5 mL)
Sterile. Preservative Free.
Record date and time of first use:

Outer label
Prod. No XXXX DIN 02510847
AstraZeneca COVID-19 Vaccine
Solution for Intramuscular Injection 5 mL
Sterile. Preservative Free.
10 Multi-dose vials (each vial contains 10 doses of 0.5 mL)
Solution pour injection intramusculaire
Stérile. Sans agent de conservation.
10 fioles multidoses (chaque fiole contient 10 doses de 0,5 mL)
AstraZeneca

Dosage and administration: See Product Monograph at www.azcovid-19.com.
Store: Refrigerated at 2 to 8°C. Do NOT freeze or shake. Keep vials in original carton to protect from light.
Discard: 6 hours after first use at room temperature (up to 30°C), or
48 hours after first use at 2 to 8°C.
Posologie et administration : Voir la monographie au www.azcovid-19.com.
Conservation : Réfrigérer entre 2 et 8 °C. NE PAS congeler ni agiter. Conserver les fioles dans la boîte d'origine pour protéger le médicament de la lumière.
Jeter : 6 heures après la première utilisation à la température ambiante (jusqu'à 30 °C), ou 48 heures après la première utilisation entre 2 et 8 °C.

Contains: L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate and water for injection. Preservative free.
Contenu : L-histidine, chlorhydrate de L-histidine monohydraté, chlorure de magnésium hexahydraté, polysorbate 80, éthanol, saccharose, chlorure de sodium, édétate disodique dihydraté et eau pour injection. Sans agent de conservation.

Questions or concerns: 1-800-668-6000
Des questions ou préoccupations? 1-800-461-3787

CANADIAN supply (5 mL – 10 doses)
For current Product Monograph use your mobile device to scan the QR code or visit www.azcovid-19.com. Pour obtenir la monographie actuelle, utilisez votre appareil mobile pour numériser le code QR ou visitez le www.azcovid-19.com. AstraZeneca Canada Inc. Mississauga, Ontario, L4Y 1M4

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ASTRAZENECA COVID-19 VACCINE

COVID-19 Vaccine (ChAdOx1-S [recombinant]),

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.

Solution for Intramuscular Injection

Multiple Dose Vial
(8 dose and 10 dose vial presentations)

Active Immunizing Agent

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 Vaccine UNDER AN INTERIM ORDER

ASTRAZENECA COVID-19 VACCINE is indicated for:

Active immunization of individuals 18 years of age and older for the prevention of coronavirus disease 2019 (COVID-19).

The use of ASTRAZENECA COVID-19 VACCINE is permitted under an interim authorization delivered in accordance with section 5 of the COVID-19 Interim order (IO)*. Patients should be advised of the nature of the authorization. The interim authorization is associated with Terms and Conditions that need to be met by the Market Authorization Holder to ascertain the continued quality, safety and efficacy of the product. For further information on authorization under this pathway, please refer to Health Canada's IO Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19.

* https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-import-sale-advertising-drugs.html#a2.8

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y 1M4
www.astrazeneca.ca

Date of Initial Authorization:
February 26, 2021

Date of Revision:
March 24, 2021

Submission Control Number: 250447 and 250727

RECENT MAJOR LABEL CHANGES

DOSAGE AND ADMINISTRATION (4.4)	03-2021
WARNINGS AND PRECAUTIONS (7)	03-2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics

The safety and efficacy of AstraZeneca COVID-19 Vaccine in children under 18 years of age have not yet been established. No data are available.

1.2 Geriatrics

Currently, there is limited information from clinical trials on the efficacy of AstraZeneca COVID-19 Vaccine in individuals ≥65 years of age. No dose adjustment is required.

2 CONTRAINDICATIONS

AstraZeneca COVID-19 Vaccine is contraindicated in individuals who are hypersensitive to the active substance or to any ingredient in the formulation. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

At the time of authorization, there are no known serious warnings or precautions associated with this product.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

AstraZeneca COVID-19 Vaccine is a solution for intramuscular injection that should be administered by a trained healthcare worker.

4.2 Recommended Dose and Dosage Adjustment

The AstraZeneca COVID-19 Vaccine vaccination course consists of two separate doses of 0.5 mL each. The second dose should be administered between 4 and 12 weeks after the first dose. Individuals should complete the vaccination course with either AstraZeneca COVID-19 Vaccine or COVISHIELD (see WARNINGS AND PRECAUTIONS).

There are no data available on the interchangeability of AstraZeneca COVID-19 Vaccine with other non ChAdOx1-S (recombinant) COVID-19 vaccines.

4.3 Reconstitution

AstraZeneca COVID-19 Vaccine **must not** be reconstituted, mixed with other

medicinal products, or diluted.

4.4 Administration

AstraZeneca COVID-19 Vaccine is a colourless to slightly brown, clear to slightly opaque solution. The vaccine should be inspected visually for particulate matter and discolouration prior to administration. Discard the vial if the solution is discoloured or visible particles are observed.

Each vaccine dose of 0.5 mL is withdrawn into a syringe for injection to be administered intramuscularly, preferably in the deltoid muscle. Use a separate sterile needle and syringe for each individual.

Each vial contains at least the number of doses stated. It is normal for liquid to remain in the vial after withdrawing the final dose. When low dead volume syringes and/or needles are used, the amount remaining in the vial may be sufficient for an additional dose. Care should be taken to ensure a full 0.5 mL dose is administered. Where a full 0.5 mL dose cannot be extracted, the remaining volume should be discarded. Do not pool excess vaccine from multiple vials.

The vaccine does not contain any preservative. After first opening, use the vial within:

- 6 hours when stored at room temperature (up to 30ºC), or
- 48 hours when stored in a refrigerator (2 to 8ºC).

The vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours. After this time, the vial must be discarded.

5 OVERDOSAGE

In the case of a suspected vaccine overdose, monitoring of vital functions and symptomatic treatment are recommended. Contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Solution Multidose vial (8 dose and 10 dose vial presentations)	• Disodium edetate dihydrate (EDTA) • Ethanol • L-Histidine • L-Histidine hydrochloride monohydrate • Magnesium chloride hexahydrate • Polysorbate 80 • Sodium chloride

		• Sucrose • Water for injection

AstraZeneca COVID-19 Vaccine is a clear to slightly opaque, colourless to slightly brown, sterile, particle free, preservative-free, solution for intramuscular injection.

One dose (0.5 ml) of AstraZeneca COVID-19 Vaccine contains:

COVID-19 Vaccine (ChAdOx1-S* recombinant) 5×10^{10} viral particles (not less than 2.5×10^{8} infectious units)
*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the unmodified SARS-CoV-2 Spike (S) glycoprotein (GP) produced in genetically modified human embryonic kidney (HEK) 293 cells by recombinant DNA technology.

AstraZeneca COVID-19 Vaccine is packaged in (not all pack sizes may be available):

- 5 mL of solution in a 10-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal).
- 4 mL of solution in a 8-dose vial (clear type I glass) with stopper (elastomeric with aluminium overseal).

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

7 WARNINGS AND PRECAUTIONS

As with any vaccine, vaccination with AstraZeneca COVID-19 Vaccine may not protect all vaccine recipients.

Individuals may not be optimally protected until after receiving the second dose of the vaccine.

General

Hypersensitivity and anaphylaxis

Hypersensitivity reactions including anaphylaxis and angioedema have occurred following administration of AstraZeneca COVID-19 Vaccine.

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Vaccine recipients should be kept under observation for at least 15 minutes after immunization.

A second dose of the vaccine should not be given to those who have experienced a hypersensitivity reaction to the first dose of AstraZeneca COVID-19 Vaccine.

Concurrent illness

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection. However, the presence of a minor infection and/or low-grade fever should not delay vaccination.

Interchangeability

There are no safety, immunogenicity or efficacy data to support interchangeability of AstraZeneca COVID-19 Vaccine with other non-ChAdOx1-S (recombinant) COVID-19 vaccines.

Driving and Operating Machinery

AstraZeneca COVID-19 Vaccine has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under **ADVERSE REACTIONS** may temporarily affect the ability to drive or use machines.

Hematologic

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with AstraZeneca COVID-19 Vaccine. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, mesenteric vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of these cases occurred within the first seven to fourteen days following vaccination. Some cases had a fatal outcome.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

As with other intramuscular injections, AstraZeneca COVID-19 Vaccine should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immune

Immunocompromised individuals

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Syncope

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

Fertility

It is unknown whether AstraZeneca COVID-19 Vaccine may impact fertility. No data are available.

7.1 Special Populations

7.1.1 Pregnant Women

The safety and efficacy of AstraZeneca COVID-19 Vaccine in pregnant women have not yet been established.

Use of AstraZeneca COVID-19 Vaccine in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AstraZeneca COVID-19 Vaccine during pregnancy. Women who are vaccinated with AstraZeneca COVID-19 Vaccine during pregnancy are encouraged to enroll in the registry by visiting https://c-viper.pregistry.com or calling 1-800-616-3791.

7.1.2 Breast-feeding

It is unknown if AstraZeneca COVID-19 Vaccine is excreted in human milk. A risk to the newborns/ infants cannot be excluded. The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for immunization against COVID-19.

7.1.3 Pediatrics

The safety and efficacy of AstraZeneca COVID-19 Vaccine in children and adolescents (under 18 years of age) have not yet been established. No data are available.

7.1.4 Geriatrics

Currently, there is limited information from clinical trials on the efficacy of AstraZeneca COVID-19 Vaccine in individuals ≥65 years of age (see ADVERSE REACTIONS and CLINICAL TRIALS section). No dose adjustment is required.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety of AstraZeneca COVID-19 Vaccine is based on an interim analysis of pooled data from four ongoing clinical trials conducted in the United Kingdom (COV001 and COV002), Brazil (COV003), and South Africa (COV005). At the time of

analysis, 23,745 participants ≥18 years of age had been randomised and received either one or two doses of AstraZeneca COVID-19 Vaccine (n=12,021) or a control treatment (n=11,724). Two doses of AstraZeneca COVID-19 Vaccine were received by 7,598 participants ages 18 to 64 and by 668 participants ages 65 and above. The median follow-up after second dose for these age groups were 63.0 days and 30.0 days, respectively.

Control treatments consisted of a licensed meningococcal vaccine (MenACWY), a saline placebo, or a combination of the two. Of the total number of control doses administered in the studies, 77.7% were MenACWY and 22.3% were saline placebo.

Demographic characteristics were generally similar among participants who received AstraZeneca COVID-19 Vaccine and those who received control. Overall, among the participants who received AstraZeneca COVID-19 Vaccine, 90.3% were aged 18 to 64 years and 9.7% were 65 years of age or older. The majority of recipients were White (75.5%), 10.1% were Black and 3.5% were Asian; 55.8% were female and 44.2% male.

Following vaccination, recipients may experience multiple adverse reactions occurring at the same time (for example, myalgia/arthralgia, headache, chills, pyrexia and malaise).

When compared with the first dose, adverse reactions reported after the second dose were generally milder and reported less frequently.

Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old).

Data is presented here for the reactogenicity subset that consists of subjects enrolled in studies COV001, COV002 and COV003 who received the standard dose for their first dose of vaccine, and who were given diary cards to record solicited adverse reactions. Data from subjects in Study COV005 were excluded from this subset due to differences in data collection. In this analysis set, 1,736 subjects (402 aged ≥65 years) received AstraZeneca COVID-19 Vaccine and 1,596 (324 aged ≥65 years) received the control.

In the reactogenicity subset, the most frequently reported adverse reactions in subjects 18 years of age and older (percentage of subjects) were injection site tenderness (75.3%), injection site pain (54.2%), fatigue (62.3%), headache (57.5%), myalgia (48.6%), malaise (44.2%), pyrexia (33.6%), chills (31.9%), arthralgia (27.0%), and nausea (21.9%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Solicited adverse reaction data were collected from Day 1 to Day 7 and reported by participants in a symptom diary card after each dose and on electronic case report forms. Reported solicited local and systemic adverse reactions are presented in Tables 1 to 4.

Table 1 – Solicited Local Adverse Events Within 7 Days After First and Second Injection by Grade-Participants 18-64 Years of Age (Dose 1 SD for Safety Analysis Set, Including Studies COV001, COV002, and COV003 Only)

Solicited Local AEs	Dose 1		Dose 2	
	Vaccine Group n(%) N= 1323	Control Group[a] n(%) N= 1260	Vaccine Group n(%) N= 567	Control Group[a] n(%) N=484
Pain				
Any Grade	798 (60.3)	468 (37.1)	195 (34.4)	158 (32.6)
Grade 3 or 4[b]	9 (0.7)	2 (0.2)	0	1 (0.2)
Tenderness				
Any Grade	1041 (78.7)	1041 (78.7)	338 (59.6)	251 (51.9)
Grade 3 or 4[b]	8 (0.6)	3 (0.2)	0	2 (0.4)
Redness				
Any Grade	35 (2.6)	23 (1.8)	6 (1.1)	4 (0.8)
>10 cm or Necrosis or ED	2 (0.2)	2 (0.2)	0	1 (0.2)
Warmth				
Any Grade	230 (17.4)	178 (14.1)	62 (10.9)	56 (11.6)
Grade 3 or 4[b]	0	0	0	0
Itch				
Any Grade	86 (6.5)	55 (4.4)	24 (4.2)	13 (2.7)
Grade 3 or 4[b]	0	0	0	0
Swelling				
Any Grade	38 (2.9)	29 (2.3)	5 (0.9)	5 (1.0)
>10 cm or PDA or Necrosis	2 (0.2)	0	0	0
Induration				
Any Grade	40 (3.0)	28 (2.2)	4 (0.7)	11 (2.3)
>10 cm or Necrosis or ED	2 (0.2)	0	0	0

[a] In Studies COV001 and COV002, MenACWY was administered as control for both Dose 1 and Dose 2. In Study COV003, MenACWY was administered as placebo for Dose 1, with a saline placebo for Dose 2.

[b] Grade 3: Unable to perform normal daily activity (COV001, COV002) or marked limitation in routine activities, some assistance usually required; medical intervention/therapy required (COV003). Grade 4: Emergency department or hospital admission required (COV001, COV002) or potentially Life-threatening: requires assessment in emergency department or hospitalization (COV003).

Note: Subjects in some study groups were recommended to take prophylactic acetaminophen 1 g every 6 hours for the first 24 hours after vaccination.

ED = exfoliative dermatitis; PDA = prevent daily activity

Table 2 – Solicited Local Adverse Events Within 7 Days After First and Second Injection by Grade-Participants ≥65 Years of Age (Dose 1 SD for Safety Analysis Set, Including Studies COV001, COV002, and COV003 Only)

Solicited Local AEs	Dose 1		Dose 2	
	Vaccine Group n(%) N=399	Control[a] n(%) N=318	Vaccine Group n(%) N=256	Control[a] n(%) N=223
Pain				
Any Grade	91 (22.8)	44 (13.8)	26 (10.2)	11 (4.9)
Grade 3 or 4[b]	0	0	0	0
Tenderness				
Any Grade	202 (50.6)	94 (29.6)	82 (32.0)	41 (18.4)
Grade 3 or 4[b]	0	0	0	0
Redness				
Any Grade	9 (2.3)	3 (0.9)	1 (0.4)	0
>10 cm or Necrosis or ED	0	0	0	0
Warmth				
Any Grade	42 (10.5)	21 (6.6)	9 (3.5)	8 (3.6)
Grade 3 or 4[b]	0	0	0	0
Itch				
Any Grade	14 (3.5)	15 (4.7)	6 (2.3)	4 (1.8)
Grade 3 or 4[b]	0	0	0	0
Swelling				
Any Grade	8 (2.0)	1 (0.3)	2 (0.8)	1 (0.4)
>10 cm or PDA or Necrosis	0	0	0	0
Induration				
Any Grade	5 (1.3)	0	1 (0.4)	0
>10 cm or Necrosis or ED	0	0	0	0

[a] In Studies COV001 and COV002, MenACWY was administered as control for both Dose 1 and Dose 2. In Study COV003, MenACWY was administered as placebo for Dose 1, with a saline placebo for Dose 2.

[b] Grade 3: Unable to perform normal daily activity (COV001, COV002) or marked limitation in routine activities, some assistance usually required; medical intervention/therapy required (COV003). Grade 4: Emergency department or hospital admission required (COV001, COV002) or potentially Life-threatening: requires assessment in emergency department or hospitalization (COV003).

Note: Subjects in some study groups were recommended to take prophylactic acetaminophen 1 g every 6 hours for the first 24 hours after vaccination.

ED = exfoliative dermatitis; PDA = prevent daily activity

Table 3 – Solicited Systemic Adverse Events Within 7 Days After First and Second Injection by Grade-Participants 18-64 Years of Age (Dose 1 SD for Safety Analysis Set, Including Studies COV001, COV002, and COV003 Only)

Solicited Systemic AEs	Dose 1		Dose 2	
	Vaccine Group n(%) N= 1323	Control Group[a] n(%) N= 1260	Vaccine Group n(%) N=573	Control Group[a] n(%) N=486
Fever				
Any Grade	152 (11.6)	5 (0.4)	4 (0.7)	3 (0.6)
Grade 3 or 4[b]	11 (0.8)	0	1 (0.2)	1 (0.2)
Feverishness				
Any Grade	509 (38.5)	124 (9.9)	68 (12.0)	33 (6.8)
Grade 3 or 4[c]	59 (4.5)	1 (0.1)	2 (0.4)	1 (0.2)
Chills				
Any Grade	492 (37.2)	96 (7.6)	37 (6.5)	26 (5.4)
Grade 3 or 4[c]	58 (4.4)	0	1 (0.2)	0
Joint pains				
Any Grade	371 (28.0)	113 (9.0)	66 (11.6)	32 (6.6)
Grade 3 or 4[c]	14 (1.1)	3 (0.2)	0	0
Muscle pains				
Any Grade	692 (52.3)	300 (23.8)	145 (25.6)	74 (15.3)
Grade 3 or 4[c]	30 (2.3)	1 (0.1)	0	0
Fatigue				
Any Grade	854 (64.6)	582 (46.2)	244 (43.0)	163 (33.7)
Grade 3 or 4[c]	53 (4.0)	7 (0.6)	6 (1.1)	3 (0.6)
Headache				
Any Grade	809 (61.1)	533 (42.3)	217 (38.3)	143 (29.5)
Grade 3 or 4[c]	38 (2.9)	6 (0.5)	2 (0.4)	1 (0.2)
Malaise				
Any Grade	634 (47.9)	233 (18.5)	122 (21.5)	65 (13.4)
Grade 3 or 4[c]	59 (4.5)	3 (0.2)	5 (0.9)	2 (0.4)
Nausea				
Any Grade	316 (23.9)	152 (12.1)	55 (9.7)	49 (10.1)
Grade 3 or 4[c]	12 (0.9)	1 (0.1)	3 (0.5)	1 (0.2)
Vomiting				
Any Grade	23 (1.7)	10 (0.8)	5 (0.9)	2 (0.4)
Grade 3 or 4[c]	4 (0.3)	1 (0.1)	2 (0.4)	0

[a] In Studies COV001 and COV002, MenACWY was administered as control for both Dose 1 and Dose 2. In Study COV003, MenACWY was administered as placebo for Dose 1, with a saline placebo for Dose 2

[b] ≥39.0°C

[c] Grade 3: Unable to perform normal daily activity (COV001, COV002) or marked limitation in routine activities, some assistance usually required; medical intervention/therapy required (COV003). Grade 4: Emergency department or hospital admission required (COV001, COV002) or potentially life-threatening: requires assessment in emergency department or hospitalization (COV003).

Note: Subjects in some study groups were recommended to take prophylactic acetaminophen 1 g every 6 hours for the first 24 hours after vaccination.

Table 4 – Solicited Systemic Adverse Events Within 7 Days After First and Second Injection by Grade-Participants ≥65 Years of Age (Dose 1 SD for Safety Analysis Set, Including Studies COV001, COV002, and COV003 Only)

Solicited Local AEs	Dose 1		Dose 2	
	Vaccine Group n(%) N=399	Control[a] n(%) N=318	Vaccine Group n(%) N=265	Control[a] n(%) N=227
Fever				
Any Grade	4 (1.0)	1 (0.3)	0	0
Grade 3 or 4[b]	0	0	0	0
Feverishness				
Any Grade	37 (9.3)	14 (4.4)	11 (4.3)	7 (3.1)
Grade 3 or 4[c]	0	0	0	0
Chills				
Any Grade	43 (10.8)	12 (3.8)	5 (2.0)	6 (2.7)
Grade 3 or 4[c]	0	0	1 (0.4)	0
Joint pains				
Any Grade	52 (13.0)	24 (7.5)	19 (7.4)	15 (6.7)
Grade 3 or 4[c]	0	0	0	0
Muscle pains				
Any Grade	90 (22.6)	36 (11.3)	35 (13.7)	19 (8.5)
Grade 3 or 4[c]	0	0	0	0
Fatigue				
Any Grade	163 (40.9)	87 (27.4)	69 (27.0)	47 (21.1)
Grade 3 or 4[c]	0	2 (0.6)	1 (0.4)	0
Headache				
Any Grade	127 (31.8)	77 (24.2)	51 (19.9)	32 (14.3)
Grade 3 or 4[c]	0	0	1 (0.4)	0
Malaise				
Any Grade	69 (17.3)	32 (10.1)	25 (9.8)	15 (6.7)
Grade 3 or 4[c]	1 (0.3)	1 (0.3)	2 (0.8)	1 (0.4)
Nausea				
Any Grade	32 (8.0)	22 (6.9)	14 (5.5)	7 (3.1)
Grade 3 or 4[c]	0	0	0	0
Vomiting				
Any Grade	1 (0.3)	2 (0.6)	0	1 (0.4)
Grade 3 or 4[c]	0	0	0	1 (0.4)

[a] In Studies COV001 and COV002, MenACWY was administered as control for both Dose 1 and Dose 2. In Study COV003, MenACWY was administered as placebo for Dose 1, with a saline placebo for Dose 2

[b] ≥39.0°C

[c] Grade 3: Unable to perform normal daily activity (COV001, COV002) or marked limitation in routine activities, some assistance usually required; medical intervention/therapy required (COV003). Grade 4: Emergency department or hospital admission required (COV001, COV002) or potentially life-threatening: requires assessment in emergency department or hospitalization (COV003).

Note: Subjects in some study groups were recommended to take prophylactic acetaminophen 1 g every 6 hours for the first 24 hours after vaccination.

Unsolicited Adverse Events

In the pooled analysis of subjects aged ≥18 who received any dose of vaccine (AstraZeneca COVID-19 Vaccine = 12,021 of whom 1169 were aged ≥65 years and control = 11,724 of whom 940 were aged ≥65 years), unsolicited adverse events occurring within 28 days after each vaccination were reported by 37.8% of participants who received AstraZeneca COVID-19 Vaccine and 27.9% of participants who received the control. Most of these events occurred within 7 days after receipt of any dose of the vaccine, with 9.4% of participants in the AstraZeneca COVID-19 Vaccine group and 9.0% of participants in the control group reporting adverse events between 7 and 28 days after any dose. The adverse events occurring in ≥ 2% participants were predominantly reactogenicity events (vaccination site pain, headache, fever, myalgia, fatigue, chills, asthenia, malaise, nausea etc).

Other unsolicited events where there was an imbalance of AEs between AstraZeneca COVID-19 Vaccine and control group and that occurred at rates >0.1% in the vaccine group included: hyperhydrosis (0.3% in the vaccine and 0.1% in the control group) and decreased appetite (0.2% in the vaccine and 0.1% in the control group).

Lymphadenopathy, pruritis and rash are recognized uncommon AEs for the MenACWY comparator vaccine. Lymphadenopathy occurred at a rate of 0.3 % in both groups. Pruritis and rash occurred at rates of 0.2% each in both the AstraZeneca COVID-19 Vaccine and control groups.

Unsolicited AEs affecting the nervous system occurred in 11.7 % of participants in the AstraZeneca COVID-19 Vaccine group and 7.8% of participants in the control group. Most of these events were due to reactogenicity, were self-limited and occurred in the first 7 days following vaccination. The events that occurred at higher rates in the AstraZeneca COVID-19 Vaccine group than the control group included headache (9.3% vs 6.1% respectively), dizziness (0.6 % vs 0.5 %) and somnolence (0.3% vs 0.2%). Facial paralysis occurred in 3 subjects in the AstraZeneca COVID-19 Vaccine group and 3 subjects in the control group, all of whom had received meningococcal vaccine.

No deaths related to the vaccine were reported in the pooled safety analysis.

Serious Adverse Events

Seventy-nine (0.7%) of subjects in the AstraZeneca COVID-19 Vaccine group and 89 (0.8%) of subjects in the control group experienced a serious adverse event between the first vaccination and the interim analysis. The median duration of follow-up from the first dose was 105 days in the AstraZeneca COVID-19 Vaccine group and 104 days in the control group.

Two serious adverse events were possibly related to the AstraZeneca COVID-19 Vaccine: one case of pyrexia (40.5°C) occurring 2 days after dose 1, and one case of transverse myelitis occurring 14 days after dose 2. Two possibly related SAEs occurred in the control group: a case of autoimmune haemolytic anemia occurring 9 days after a single dose of the MenACWY vaccine and one case of myelitis occurring 54 days after a single dose of MenACWY.

8.3 Post-Market Adverse Reactions

The following adverse reactions have been spontaneously reported during worldwide post-authorization use of AstraZeneca COVID-19 Vaccine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. They are included because: a) they represent reactions that are known to occur following immunizations generally; or b) they are potentially serious; or c) on the basis of their frequency of reporting.

Immune system disorders: Anaphylactic reaction.

Skin and subcutaneous tissue disorders: Angioedema.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with AstraZeneca COVID-19 Vaccine. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, mesenteric vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. See **WARNINGS AND PRECAUTIONS**.

9 DRUG INTERACTIONS

No interaction studies have been performed.

Do not mix AstraZeneca COVID-19 Vaccine with other vaccines/products in the same syringe.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

AstraZeneca COVID-19 Vaccine is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralising antibody and cellular immune responses, which may contribute to protection to COVID-19.

11 STORAGE, STABILITY AND DISPOSAL

Unopened multidose vial

Store in a refrigerator (2 to 8ºC).

Do not freeze.

Store in outer carton in order to protect from light.

Use the product before the expiration date on the vial label.

Opened multidose vial

For storage conditions after first opening of the medicinal product, see below.

After first opening, chemical and physical in-use stability has been demonstrated from the time of vial puncture to administration for no more than:

- 6 hours at room temperature, up to 30ºC, or
- 48 hours in a refrigerator (2 to 8ºC).

The vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal

AstraZeneca COVID-19 Vaccine contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: COVID-19 Vaccine (ChAdOx1-S [recombinant])

Product Characteristics:

AstraZeneca COVID-19 Vaccine is a clear to slightly opaque, colourless to slightly brown, sterile, particle free, pH 6.6, preservative-free, solution for intramuscular injection.

One dose (0.5 ml) of AstraZeneca COVID-19 Vaccine contains:

COVID-19 Vaccine (ChAdOx1-S* recombinant) 5×10^{10} viral particles

*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the unmodified SARS-CoV-2 Spike (S) glycoprotein (GP) produced in genetically modified human embryonic kidney (HEK) 293 cells by recombinant DNA technology.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Interim analysis of pooled data from COV001, COV002, COV003, and COV005

AstraZeneca COVID-19 Vaccine has been evaluated based on an interim analysis of pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study in healthy adults 18 to 55 years of age in the UK (COV001; NCT04324606), a Phase II/III Study in adults ≥18 years of age in the UK (COV002; NCT04400838), a Phase III Study in adults ≥18 years of age in Brazil (COV003; ISRCTN89951424), and a Phase I/II study in adults aged 18 to 65 years of age in South Africa (COV005; NCT04444674). The studies excluded participants with a history of anaphylaxis or angioedema; participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, or neurological illnesses; pregnant or breastfeeding women; participants with known history of SARS-CoV-2 infection as well as those with severe immunosuppression.

The primary efficacy endpoint was virologically-confirmed symptomatic cases of COVID-19* confirmed by a clinical adjudication committee.

**PCR confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥37.8 °C), cough, shortness of breath, anosmia, or ageusia.*

Based on the pre-defined criteria for the interim efficacy analysis (data cut-off November 4, 2020), COV002 and COV003 exceeded the threshold of ≥5 adjudication committee confirmed COVID-19 cases per study and therefore contributed to the efficacy analysis; COV001 and COV005 did not exceed such threshold and were

excluded from this interim analysis. In the pooled analysis for efficacy (COV002 and COV003), participants ≥18 years of age that received two doses of AstraZeneca COVID-19 Vaccine or control (meningococcal vaccine or saline placebo) were included. The planned dose was 5×10^{10} viral particles (vp) per dose administered via IM injection. The population used for the interim analysis of the primary efficacy endpoint included participants who received two doses of the AstraZeneca COVID-19 Vaccine or control and did not have evidence of prior infection with SARS-CoV-2 through 15 days after the second dose. Study COV002 contributed a total of 7548 participants (3744 receiving the AstraZeneca COVID-19 Vaccine, 3804 receiving two doses of a meningococcal vaccine control) and Study COV003 contributed a total of 4088 participants (2063 receiving the AstraZeneca COVID-19 Vaccine, 2025 receiving meningococcal vaccine followed by saline placebo control) to this analysis.

Participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.

Table 5 – Demographic Characteristics – Subjects Without Evidence of Infection Prior to 15 Days After Dose 2 – Evaluable Efficacy Population (COV002 and COV003)

Characteristic	Study COV002 (United Kingdom)		Study COV003 (Brazil)	
	AstraZeneca COVID-19 Vaccine (N=3744)	Meningococcal Vaccine (N=3804)	AstraZeneca COVID-19 Vaccine (N=2063)	Meningococcal Vaccine/ Placebo (N=2025)
Sex				
Female	2264 (60.5)	2365 (62.2)	1261 (61.1)	1156 (57.1)
Male	1480 (39.5)	1438 (37.8)	802 (38.9)	869 (42.9)
Age (years)				
Mean (SD)	43.0 (13.1)	43.2 (13.0)	38.9 (11.5)	38.6 (11.2)
Median	42	42	37	36
Min, max	18, 86	18, 88	19, 84	18, 77
Age group				
18 to 64 years	3467 (92.6)	3525 (92.7)	1999 (96.9)	1985 (98.0)
≥65 years	277 (7.4)	279 (7.3)	64 (3.1)	40 (2.0)
Race				
White	3450 (92.1)	3534 (92.9)	1357 (65.8)	1366 (67.5)
Asian	213 (5.7)	197 (5.2)	54 (2.6)	53 (2.6)
Black	23 (0.6)	16 (0.4)	230 (11.1)	210 (10.4)
Other	22 (0.6)	19 (0.5)	260 (12.6)	260 (12.8)
Mixed	34 (0.9)	37 (1.0)	159 (7.7)	133 (6.6)
Not reported	2 (0.1)	1 (<0.1)	3 (0.1)	3 (0.1)
Comorbidity at baseline[a]				

Table 5 – Demographic Characteristics – Subjects Without Evidence of Infection Prior to 15 Days After Dose 2 – Evaluable Efficacy Population (COV002 and COV003)

Characteristic	Study COV002 (United Kingdom)		Study COV003 (Brazil)	
	AstraZeneca COVID-19 Vaccine (N=3744)	Meningococcal Vaccine (N=3804)	AstraZeneca COVID-19 Vaccine (N=2063)	Meningococcal Vaccine/ Placebo (N=2025)
Yes	1311 (35.0)	1398 (36.8)	759 (36.8)	735 (36.3)
No	2432 (65.0)	2401 (63.1)	1301 (63.1)	1282 (63.3)
Missing	1 (<0.1)	5 (0.1)	3 (0.1)	8 (0.4)

[a] Number (%) of subjects who have 1 or more of that following comorbidities at baseline that increase the risk of sever COVID19 disease: BMI $\geq$30 kg/m^2, cardiovascular disorder, respiratory disease, or diabetes.

14.2 Study Results

The interim analysis of the primary efficacy endpoint (data cut-off November 4, 2020) included 11,636 participants 18 years of age and older (5,807 in the AstraZeneca COVID-19 Vaccine group and 5,829 in the control group). At the time of the interim analysis, participants had been followed for symptomatic COVID 19 disease for a median of 63 days (range: 16-94 days) after the second dose, corresponding to exposure of 921 person-years in the AstraZeneca COVID-19 Vaccine and 925 person-years in the control group.

Participants randomised to AstraZeneca COVID-19 Vaccine received either two standard doses [SD] (5×10^{10} vp per dose) (SD/SD) or, due to a difference in concentration determination between two analytical methods, one low dose [LD] (2.2×10^{10} vp) followed by one SD (5×10^{10} vp) (LD/SD).

The interval between dose 1 and dose 2 ranged from 3 to 26 weeks for these data. In these 11,636 seronegative participants, 86 (0.7%) had a dose interval of less than 4 weeks, 8,786 (75.5%) had a dose interval of 4-12 weeks and 2,764 (23.8%) had a dose interval of more than 12 weeks.

A total of 131 participants had SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose. There were 30 confirmed COVID-19 cases identified in the AstraZeneca COVID-19 Vaccine group and 101 in the control group, respectively, for the primary interim efficacy analysis. Compared to control, efficacy of AstraZeneca COVID-19 Vaccine in participants with first COVID-19 occurrence from 15 days after Dose 2 was 70.42% (two-sided 95.84% confidence interval of 58.84% to 80.63%, p<0.001). There were no cases of COVID-19 hospitalisation (WHO severity score ≥4) in the participants that received AstraZeneca COVID-19 Vaccine as compared to 5 cases in control participants.

The vaccine efficacy was based on pre-specified analysis; however the results should be interpreted with caution given that it excludes 51% of randomized and vaccinated subjects, the majority of which had only received a single dose. In addition, a significant difference was observed in vaccine efficacy between the LD/SD cohort and the SD/SD cohort. The findings may also be confounded by the variability in dosing interval.

In participants who received two standard doses of the vaccine (SD/SD) or the corresponding control (4,440 in the AstraZeneca COVID-19 Vaccine group and 4,455 in the control group), a total of 98 participants had SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose (27 cases in the AstraZeneca COVID-19 Vaccine group and 71 cases in the control group). In this population, vaccine efficacy from 15 days post second dose was 62.10% (two-sided 95% confidence interval of 39.96% to 76.08%).

Evidence shows protection starts from approximately 3 weeks after first dose of vaccine and persists up to 12 weeks. A second dose should be given at a 4-to-12-week interval after the first dose, with evidence that efficacy increases with longer dosing intervals.

Based on an updated analysis (data cut-off December 7, 2020), vaccine efficacy was 59.5% (two-sided 95% confidence interval of 45.8% to 69.7%) in participants who received two standard doses with the second dose administered 4 to 12 weeks after the first dose. Regarding COVID-19 hospitalisation (WHO severity score ≥4) in these data, there were 0 (0.0%; N=5,258) cases of COVID-19 hospitalisation in participants who received two doses of AstraZeneca COVID-19 Vaccine (≥15 days post dose 2) as compared to 8 (0.2%; N=5,210) for control, including one severe case (WHO severity score ≥6), reported for control and 0 severe cases reported for AstraZeneca COVID-19 Vaccine.

At the time of interim analysis, there were limited number of COVID-19 cases in participants ≥65 years old.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Intramuscular administration of AstraZeneca COVID-19 Vaccine at a dose of $3.7x10^{10}$ vp/animal once weekly for 3 weeks (total of 3 doses) resulted in transient inflammation

at the site of injection and underlying fascia and connective tissue, increase in body temperature, and increased spleen weights, decreased monocyte counts, and clinical chemistry changes indicative of an active phase response.

Full recovery from all findings was observed following a 28-day recovery period. These changes are consistent with an expected immunostimulatory response following intramuscular administration of a vaccine.

Carcinogenicity

AstraZeneca COVID-19 Vaccine has not been evaluated for carcinogenicity in animals, as carcinogenicity studies were not considered relevant to this vaccine.

Genotoxicity

AstraZeneca COVID-19 Vaccine has not been evaluated for genotoxicity, as genotoxicity studies were not considered relevant to this vaccine.

Reproductive and Developmental Toxicology

A definitive reproductive and developmental toxicity study in animals has not yet been completed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

AstraZeneca COVID-19 Vaccine

COVID-19 Vaccine (ChAdOx1-S [recombinant]), Solution for Intramuscular Injection

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.

Health Canada has authorized the sale of this COVID-19 vaccine under an Interim Order. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about AstraZeneca COVID-19 Vaccine.

What is AstraZeneca COVID-19 Vaccine used for?

AstraZeneca COVID-19 Vaccine is a vaccine used to prevent the coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus. It can be given to adults 18 years of age and older.

How does AstraZeneca COVID-19 Vaccine work?

COVID-19 is caused by a virus called coronavirus (SARS-CoV-2).

AstraZeneca COVID-19 Vaccine stimulates the body's natural defences (immune system), by causing the body to produce its own protection (antibodies) against the SARS-CoV-2 virus that causes the COVID-19 infection.

The vaccine is given by injection with a needle in the upper arm and will require two doses given between 4 and 12 weeks apart. As with any vaccine, AstraZeneca COVID-19 Vaccine may not fully protect all those who receive it.

Even after you have had both doses of the vaccine, continue to follow the recommendations of local public health officials to prevent spread of COVID-19.

Individuals may not be optimally protected until after receiving the second dose of the vaccine.

You cannot get COVID-19 from this vaccine.

What are the ingredients in AstraZeneca COVID-19 Vaccine?

Medicinal ingredients: ChAdOx1-S [recombinant]

Non-medicinal ingredients:

- Ethanol,
- Disodium edetate dihydrate (EDTA),
- L-Histidine,
  L-Histidine hydrochloride monohydrate,
- Magnesium chloride hexahydrate,

- Polysorbate 80,
- Sodium chloride,
- Sucrose,
- Water for injection

AstraZeneca COVID-19 Vaccine comes in the following dosage forms:

Clear to opalescent, colourless to slightly brown, particle-free, preservative-free, solution for injection. It is provided in a multiple dose vial of 10 or 8 doses, one dose is 0.5 mL.

You should not receive AstraZeneca COVID-19 Vaccine if you:

- Had a severe allergic reaction to any of the medicinal ingredients or any of the other ingredients in this vaccine (see ***What are the ingredients in AstraZeneca COVID-19 Vaccine***). If you are not sure, talk to your healthcare professional;
- Have had an allergic reaction to a previous dose of AstraZeneca COVID-19 Vaccine;
- Have any symptoms that could be due to COVID-19. Talk with your healthcare professional about your symptoms and getting a COVID-19 test. Your healthcare professional will advise you when you are able to receive the vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AstraZeneca COVID-19 Vaccine. Talk about any health conditions or problems you may have, including if you:

- Have any allergies or previous problems following administration of AstraZeneca COVID-19 Vaccine such as an allergic reaction or breathing problems;
- Have had a severe allergic reaction after any other vaccine injection;
- Have a weakened immune system due to a medical condition (immunodeficiency) or are on a medicine that affects your immune system (such as high-dose corticosteroids, immunosuppressants or cancer medicines);
- Currently have a severe infection with a high temperature (over 38°C);
- Have a problem with bleeding or bruising, or if you are taking a blood thinning medicine (anticoagulant);
- Are pregnant, think you may be pregnant or plan to become pregnant;
- Are breastfeeding or plan to breastfeed.

If you are not sure if any of the above applies to you, talk to your healthcare professional before you are given the vaccine.

A combination of blood clots and low level of platelets, in some cases together with bleeding, has been observed very rarely following vaccination with AstraZeneca COVID-19 Vaccine. Seek immediate medical attention if you develop shortness of breath, chest pain, leg swelling, or persistent abdominal pain following vaccination. Also, seek immediate medical attention if you experience after a few days severe or persistent headaches or blurred vision, or experience skin bruising or pinpoint round spots beyond the site of vaccination which appears after a few days.

Driving and using machines

AstraZeneca COVID-19 Vaccine has no known effect on the ability to drive and use machines. However, side effects listed in ***What are possible side effects from using AstraZeneca COVID-19 Vaccine*** may impact your ability to drive and use machines. If you feel unwell, do

not drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Tell your healthcare professional if you are taking, have recently taken or might take, any other medicines or vaccines.

How AstraZeneca COVID-19 Vaccine is given:

- A healthcare provider will inject the vaccine into a muscle (intramuscular injection) in your upper arm.
- During and after each injection of the vaccine, your doctor, pharmacist or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

Usual dose:

You will receive 2 injections. You will be told when you need to return for your second injection of AstraZeneca COVID-19 Vaccine.

The second injection can be given between 4 and 12 weeks after the first injection.

It is very important that you return for the second injection, or the vaccine may not work as well.

Individuals should complete the vaccination course with either AstraZeneca COVID-19 Vaccine or COVISHIELD.

Overdose:

In the event of suspected overdose with AstraZeneca COVID-19 Vaccine, contact your regional poison control centre.

Missed Dose:

If you forget to go back to your healthcare professional at the scheduled time for your next dose, ask your healthcare professional for advice. It is important that you return for your second injection of AstraZeneca COVID-19 Vaccine.

What are possible side effects from using AstraZeneca COVID-19 Vaccine?

Like all medicines, AstraZeneca COVID-19 Vaccine can cause side effects, although not everybody gets them.

Should you develop any serious symptoms or symptoms that could be an allergic reaction, seek medical attention right away. Symptoms of an allergic reaction include:

- hives (bumps on the skin that are often very itchy)
- feeling faint or light-headed
- changes in your heartbeat
- swelling of your face, lips, tongue or throat
- difficulty breathing, shortness of breath or wheezing

In clinical studies, most side effects were mild to moderate in nature and resolved within a few days. Fewer side effects were reported after the second dose.

After vaccination, you may have more than one side effect at the same time (for example, muscle/joint aches, headaches, chills and generally feeling unwell). If any of your symptoms are persistent, please seek advice from your healthcare professional.

Side effects that occurred during clinical trials with AstraZeneca COVID-19 Vaccine were as follows:

Very Common (may affect more than 1 in 10 people)

- tenderness, pain, warmth, or itching where the injection is given
- generally feeling unwell
- feeling tired (fatigue)
- chills or feeling feverish
- headache
- feeling sick (nausea)
- joint pain or muscle ache

Common (may affect up to 1 in 10 people)

- swelling or redness where the injection is given
- fever
- being sick (vomiting) or diarrhea
- pain in legs or arms
- flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills

Uncommon (may affect up to 1 in 100 people)

- sleepiness or feeling dizzy
- decreased appetite
- abdominal pain
- enlarged lymph nodes
- excessive sweating, itchy skin, rash or hives

Not known (the frequency cannot be determined from the available data)

- severe allergic reaction (anaphylaxis)
- severe swelling of the lips, mouth, throat (which may cause difficulty in swallowing or breathing)

These are not all the possible side effects you may have when taking AstraZeneca COVID-19 Vaccine. If you experience any side effects not listed here, tell your healthcare professional.

If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and AstraZeneca Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:

Your healthcare professional is responsible for storing this vaccine and disposing of any unused product correctly.

Keep out of reach and sight of children.

If you want more information about AstraZeneca COVID-19 Vaccine:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.astrazeneca.ca, or www.azcovid-19.com, or by calling 1-800-668-6000.

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