PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

COVISHIELD

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

COVISHIELD (manufactured by Serum Institute of India) and AstraZeneca COVID-19 VACCINE (manufactured by AstraZeneca) 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
(each vial contains 10 doses of 0.5 mL)

Active Immunizing Agent

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 Vaccine UNDER AN INTERIM ORDER
COVISHIELD 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 COVISHIELD 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/drugsvaccines-treatments/interim-order-import-sale-advertising-drugs.html#a2.8

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Submission Control Number: 248651

RECENT MAJOR LABEL CHANGES

Not applicable.

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

COVISHIELD (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).

1.1 Pediatrics

The safety and efficacy of COVISHIELD 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 COVISHIELD in individuals ≥65 years of age. No dose adjustment is required.

2 CONTRAINDICATIONS

COVISHIELD 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

COVISHIELD is a solution for intramuscular injection that should be administered by a trained healthcare worker.

4.2 Recommended Dose and Dosage Adjustment

The COVISHIELD 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 COVISHIELD or AstraZeneca COVID-19 Vaccine (see **WARNINGS AND PRECAUTIONS**).

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

4.3 Reconstitution

COVISHIELD **must not** be reconstituted, mixed with other medicinal products, or

diluted.

4.4 Administration

COVISHIELD is a colourless to slightly clear to slightly opaque solution essentially free from visible particles. 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. It is normal for liquid to remain in the vial after withdrawing the final dose.

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

- 6 hours when stored at room temperature (up to 25ºC), 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 (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

COVISHIELD is a clear to slightly opaque, colourless to slightly opaque solution essentially free from visible particles, preservative-free, solution for intramuscular injection.

One dose (0.5 ml) of COVISHIELD contains:

COVID-19 Vaccine (**ChAdOx1-S*** **[recombinant]**) 5 x 10^{10} viral particles (not less than 2.5 x 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.

COVISHIELD is packaged in:

- 5 mL of solution in a 10-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 COVISHIELD 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

As with all injectable vaccines, 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.

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 COVISHIELD with other non-ChAdOx1-S (recombinant) COVID-19 vaccines.

Driving and Operating Machinery

COVISHIELD 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

As with other intramuscular injections, COVISHIELD 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 COVISHIELD may impact fertility. No data are available.

7.1 Special Populations

7.1.1 Pregnant Women

The safety and efficacy of COVISHIELD in pregnant women have not yet been established.

Use of COVISHIELD in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks.

7.1.2 Breast-feeding

It is unknown if COVISHIELD 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 COVISHIELD 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 COVISHIELD 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.

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%).

A supportive COVISHIELD comparative safety and immunogenicity study was conducted in India. Among the participants who received COVISHIELD, 87.33% were aged 18 to 59 years and 12.67% were 60 years of age or older. An interim, unplanned analysis included data collected on 1181 (98.3%) participants who received the second

dose of COVISHIELD. The immunogenicity (as measured by binding IgG antibodies against SARS-CoV-2 spike protein) and safety profile of COVISHIELD appeared to be comparable to that of the AstraZeneca COVID-19 vaccine.

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] $\geq$39.0^{o}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.

9 DRUG INTERACTIONS

No interaction studies have been performed.

Do not mix COVISHIELD with other vaccines/products in the same syringe.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

COVISHIELD 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

COVISHIELD 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:

COVISHIELD is a clear to slightly opaque solution essentially free from visible particles, sterile, , pH 6.6, preservative-free, solution for intramuscular injection.

One dose (0.5 ml) of COVISHIELD 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Authorization of COVISHIELD was based on its comparability to the AstraZeneca COVID-19 Vaccine as determined by evaluation and direct comparison of manufacturing processes and controls and the quality characteristics of the two products. The results of this comparison determined that the two products were sufficiently similar that the efficacy, immunogenicity and safety of COVISHIELD could be inferred from the non-clinical and clinical studies from the AstraZeneca vaccine.

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

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)
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]				
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 severe COVID19 disease: BMI ≥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 x 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.

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 COVISHIELD 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

COVISHIELD has not been evaluated for carcinogenicity in animals, as carcinogenicity studies were not considered relevant to this vaccine.

Genotoxicity

COVISHIELD 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

COVISHIELD

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

COVISHIELD (manufactured by Serum Institute of India) and AstraZeneca COVID-19 VACCINE (manufactured by AstraZeneca) 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 COVISHIELD.

What is COVISHIELD used for?

COVISHIELD 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 COVISHIELD work?

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

COVISHIELD 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, COVISHIELD 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 COVISHIELD?

Medicinal ingredients: COVID-19 Vaccine 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

COVISHIELD comes in the following dosage forms:

Clear to slightly opaque solution essentially free from visible particles, preservative-free, solution for injection. It is provided in a multiple dose vial of 10 doses; one dose is 0.5 mL.

You should not receive COVISHIELD 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 COVISHIELD***). If you are not sure, talk to your healthcare professional;
- Have had an allergic reaction to a previous dose of COVISHIELD;
- 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 COVISHIELD. Talk about any health conditions or problems you may have, including if you:

- Have any allergies or previous problems following administration of COVISHIELD such as an allergic reaction or breathing problems;
- Have had a severe allergic reaction (anaphylaxis) 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.

Driving and using machines

COVISHIELD has no known effect on the ability to drive and use machines. However, side effects listed in ***What are possible side effects from using COVISHIELD*** 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 COVISHIELD 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**.**

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 COVISHIELD or AstraZeneca COVID-19 Vaccine.

Overdose:

In the event of suspected overdose with COVISHIELD, 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.

What are possible side effects from using COVISHIELD?

Like all medicines, COVISHIELD can cause side effects, although not everybody gets them. In clinical studies with the vaccine, most side effects were mild to moderate in nature and resolved within a few days. If you notice any side effects not mentioned in this leaflet, please inform your healthcare professional.

Side effects that occurred during clinical trials with COVISHIELD were as follows:

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

- tenderness, pain, warmth, redness, itching or swelling 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)

- fever
- being sick (vomiting) or diarrhea

Uncommon (may affect up to 1 in 100 people)

- sleepiness or feeling dizzy
- decreased appetite

- enlarged lymph nodes
- excessive sweating, itchy skin or rash

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

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)
- swelling of the face, tongue or throat
- difficulty breathing

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 Verity Pharmaceuticals 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 COVISHIELD:

- 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.veritypharma.com, or www.covishield-canada.ca, or by calling 1-800-977-9778.

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