AstraZeneca Sdn Bhd
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23 August 2021

Dear Healthcare Professional,

CONDITIONAL REGISTRATION OF COVID-19 VACCINE ASTRAZENECA SOLUTION FOR INJECTION WITH EXEMPTIONS FROM MALAYSIA SPECIFIC LABELLING REQUIREMENTS

With regards to the matter above, AstraZeneca would like to inform that the approval in Malaysia is supported by common pack product label and carton to facilitate supply during pandemic period. In order to make the artwork acceptable to multiple countries around the world during the pandemic the artwork is exempted from a number of country specific labelling requirements. There will not be country-specific packs for Malaysia until the post pandemic period which has not been determined yet.

2. Enclosed are the additional Malaysian local labelling information for your reference which will not be included in the artwork during the pandemic period.

Immediate label

Product Information	**Details**
Product Name	COVID-19 Vaccine AstraZeneca Solution for Injection
Strength of active substance	1 x 10^11 vp/ml
Name and content of alcohol	Ethanol 2 mg per 0.5 ml dose

Outer Carton

Product Information	**Details**
Name and content of alcohol	This medicinal product contains 2 mg of alcohol (ethanol) per 0.5 ml dose.
Disposal	COVID-19 Vaccine AstraZeneca 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.
Keep out of the sight and reach of children	Jauhi dari pandangan dan jangkauan kanak-kanak
Strength of active substance	1 x 10^11 vp/ml
Batch Releaser	SK Bioscience Co Limited (No.97), 150, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, Republic of Korea
Local Registration Number (MAL Number)	To be updated
Product Registration Holder	AstraZeneca Sdn Bhd (69730-X)

AstraZeneca Sdn Bhd
Nucleus Tower, Level 12
No. 10, Jalan PJU 7/6, Mutiara Damansara
47800 Petaling Jaya, Selangor, Malaysia
Company Regn No. 69730-X

(PRH)	Level 11 & 12, Nucleus Tower, No. 10, Jalan PJU 7/6, Mutiara Damansara, 47800 Petaling Jaya, Selangor, Malaysia
Others	Controlled Medicine

4. Any future labelling updates will be submitted to the National Pharmaceutical Regulatory Division (NPRA) for review and approval before implementation on packs.

Thank you.

Yours sincerely,
Angie Ng Xiao Wei
Regulatory Affairs
AstraZeneca Sdn. Bhd.

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DISCLAIMER: THIS PRODUCT IS APPROVED UNDER MALAYSIA CONDITIONAL REGISTRATION FOR PHARMACEUTICAL PRODUCTS DURING DISASTER GUIDELINE. THE ADMINISTRATION OF THE PRODUCT IS PURELY BASED ON INDIVIDUAL'S PREFERENCE

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions.

This product information will be updated on a regular basis as further data and safety reports become available.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:
COVID-19 Vaccine (ChAdOx1-S* recombinant) 5×10^{10} viral particles (vp)
*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is colourless to slightly brown, clear to slightly opaque and particle free with a pH of 6.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.
The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Individuals 18 years of age and older
The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose (see section 5.1). There are no data available on the interchangeability of COVID-19 Vaccine AstraZeneca with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of COVID-19 Vaccine AstraZeneca should receive the second dose of COVID-19 Vaccine AstraZeneca to complete the vaccination course.

Elderly population
No dose adjustment is required. See also section 4.4 and 5.1.

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

Method of administration
COVID-19 Vaccine AstraZeneca is for intramuscular injection only, preferably in the deltoid muscle of the upper arm. Do not inject the vaccine intravascularly, subcutaneously or intradermally. The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions on handling and disposal, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine AstraZeneca.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

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.

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first fourteen days following vaccination and occurred mostly in women under 60 years of age.

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.

Risk of bleeding with intramuscular administration
As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine AstraZeneca may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

Protection starts from approximately 3 weeks after the first dose of COVID-19 Vaccine AstraZeneca. Individuals may not be fully protected until 15 days after the second dose is administered. As with all vaccines, vaccination with COVID-19 Vaccine AstraZeneca may not protect all vaccine recipients (see section 5.1).

Currently available clinical trial data do not allow an estimate of vaccine efficacy in subjects over 55 years of age.

Excipients

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 ml dose, that is to say essentially “sodium-free”.

Ethanol
This medicinal product contains 2 mg of alcohol (ethanol) per 0.5 ml dose. The small amount of alcohol in this medicinal product will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of COVID-19 Vaccine AstraZeneca with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of COVID-19 Vaccine AstraZeneca in pregnant women.

Animal reproductive toxicity studies have not been completed. Based upon results from the preliminary study, no effects are expected on development of the fetus (see section 5.3).

Administration of COVID-19 Vaccine AstraZeneca during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

It is unknown whether COVID-19 Vaccine AstraZeneca is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

COVID-19 Vaccine AstraZeneca has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety of COVID-19 Vaccine AstraZeneca is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,021 received at least one dose of COVID-19 Vaccine AstraZeneca and 8,266 received two doses. The median duration of follow-up was 62 days post-dose 2.

The most frequently reported adverse reactions were injection site tenderness (63.7%), injection site pain (54.2%), headache (52.6%), fatigue (53.1%), myalgia (44.0%), malaise (44.2%), pyrexia (includes feverishness (33.6%) and fever >38°C (7.9%)), chills (31.9%), arthralgia (26.4%) and nausea (21.9%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

Reactogenicity was generally milder and reported less frequently in older adults (≥65 years old).

The safety profile was consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline; the number of seropositive participants at baseline was 718 (3.0%).

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data); within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness.

Table 1 Adverse drug reactions

MedDRA SOC	**Frequency**	**Adverse Reactions**
Blood and lymphatic system disorders	Common	Thrombocytopenia
	Uncommon	Lymphadenopathy
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Metabolism and nutrition disorders	Uncommon	Decreased appetite

MedDRA SOC	Frequency	Adverse Reactions
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness Somnolence
Vascular disorders	Very rare	Thrombosis in combination with thrombocytopenia*
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis Pruritus Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site tenderness Injection site pain Injection site warmth Injection site pruritus Injection site bruising[a] Fatigue Malaise Feverishness Chills
	Common	Injection site swelling Injection site erythema Fever[b]

[a] Injection site bruising includes injection site haematoma (uncommon)
[b] Measured fever ≥38°C
*Severe and very rare cases of thrombosis in combination with thrombocytopenia have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the NPRA website and include batch/Lot number if available.

4.9 Overdose

Experience of overdose is limited.
There is no specific treatment for an overdose with COVID-19 Vaccine AstraZeneca. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, other viral vaccines, ATC code: J07BX03

Mechanism of action

COVID-19 Vaccine AstraZeneca 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.

Clinical efficacy

Analysis of pooled data from COV002 and COV003

The clinical efficacy of COVID-19 Vaccine AstraZeneca has been evaluated based on an analysis of pooled data from two on-going randomised, blinded, controlled trials: a phase II/III study, COV002, in adults ≥18 years of age (including the elderly) in the UK; and a phase III study, COV003, in adults ≥18 years of age (including the elderly) in Brazil. The studies excluded participants with severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with severe immunosuppression, pregnant women and participants with a known history of SARS-CoV-2 infection. Influenza vaccines could be administered 7 days before or after any dose of COVID-19 Vaccine AstraZeneca. All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.

In the pooled analysis for efficacy, participants ≥18 years of age received two doses (5×10^{10} viral particles per dose corresponding to not less than 2.5×10^{8} infectious units) of COVID-19 Vaccine AstraZeneca (N=6,106) or control (meningococcal vaccine or saline) (N=6,090), administered via IM injection.

Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 3 to 23 weeks (21 to 159 days), with 86.1% of participants receiving their two doses within the interval of 4 to 12 weeks (28 to 84 days).

Baseline demographics were well balanced across COVID-19 Vaccine AstraZeneca and control treatment groups. In the pooled analysis, among the participants who received COVID-19 Vaccine AstraZeneca with a dose interval of between 4 and 12 weeks, 87.0% of participants were 18 to 64 years old (with 13.0% aged 65 or older and 2.8% aged 75 or older); 55.1% of subjects were female; 76.2% were White, 6.4% were Black and 3.4% were Asian. A total of 2,068 (39.3%) participants had at least one pre-existing comorbidity (defined as a BMI ≥30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes). At the time of analysis the median follow up time post-dose 2 was 78 days.

Final determination of COVID-19 cases were made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of 218 participants had SARS-CoV-2 virologically confirmed COVID-19 occurring ≥15 days post second dose with at least one COVID-19 symptom (objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-CoV-2 infection. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2).

Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95% CI)[b]
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Licensing regimen					
4 – 12 weeks (28 to 84 days)	5,258	64 (1.2)	5,210	154 (3.0)	59.5 (45.8, 69.7)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval;

[a] Efficacy endpoint was based on confirmed COVID-19 cases in subjects aged 18 years and over who were seronegative at baseline, who had received two doses and were on-study ≥15 days post second dose.

[b] CI not adjusted for multiplicity.

Vaccine efficacy was 62.6% (95% CI: 50.9; 71.5) in participants receiving two recommended doses with any dose interval (ranging from 3 to 23 weeks), in a pre-specified analysis.

Regarding COVID-19 hospitalisation (WHO Severity grading ≥4) there were 0 (0.0%; N=5,258) cases of COVID-19 hospitalisation in participants who received two doses of COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) as compared to 8 (0.2%; N=5,210) for control, including one severe case (WHO Severity grading ≥6), reported for control. In all participants who received at least one dose, as from 22 days post dose 1, there were 0 (0.0%, N=8,032) cases of COVID-19 hospitalisation in participants who received COVID-19 Vaccine AstraZeneca, as compared to 14 (0.2%, N=8,026), including one fatality, reported for control.

Participants who had one or more comorbidities had a vaccine efficacy of 58.3% [95% CI: 33.6; 73.9]; 25 (1.2%) vs 60 (2.9%) for COVID-19 Vaccine AstraZeneca (N=2,068) and control (N=2,040), respectively; which was similar to the vaccine efficacy observed in the overall population.

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 (see section 4.4).

Elderly population

Among participants aged between 56 and 65 years old, 8 cases of COVID-19 were reported in those receiving COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) compared with 9 cases for control; 2 and 6 cases of COVID-19 were reported in participants older than 65 years of age, for COVID-19 Vaccine AstraZeneca (≥15 days post dose 2) and control, respectively.

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine are not expected to have genotoxic potential.

Reproductive toxicity

Animal studies of potential toxicity to reproduction and development have not yet been completed. A preliminary reproductive toxicity study in mice does not show toxicity in dams or foetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

Unopened vial

6 months when stored in a refrigerator (2°C – 8°C)

Opened vial

Chemical and physical in-use stability have been demonstrated from the time of vial opening (first needle puncture) to administration for no more than 48 hours in a refrigerator (2°C – 8°C). Within this time period the product may be kept and used at temperatures up to 30°C for a single period of up to 6 hours. After this time period, the product must be discarded. Do not return it to the refrigerator.

From a microbiological point of view, after first opening the vaccine should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened multidose vial
Store in a refrigerator (2 to 8°C).
Do not freeze.
Keep vials in outer carton to protect from light.

After first use
For storage conditions after first use of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Multidose vial

- 5 ml of solution in a 10-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap. Packs of 10 vials.
- 4 ml of solution in an 8-dose vial (clear type I glass) with a halobutyl rubber stopper and an aluminium overseal with a plastic flip-off cap. Packs of 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions and administration

This vaccine should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

Do not use this vaccine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Unopened multidose vial should be stored in a refrigerator (2°C – 8°C). Do not freeze.

Keep the vials in outer carton in order to protect from light.

The vaccine should be inspected visually for particulate matter and discolouration prior to administration. COVID-19 Vaccine AstraZeneca is a colourless to slightly brown, clear to slightly opaque solution. Discard the vial if the solution is discoloured or visible particles are observed. Do not shake. Do not dilute the solution.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

The COVID-19 Vaccine AstraZeneca 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 who have received the first dose of COVID-19 Vaccine AstraZeneca should receive the second dose of the same vaccine to complete the vaccination course.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly, preferably in the deltoid muscle of the upper arm. Use a new needle for administration, when possible.

It is normal for liquid to remain in the vial after withdrawing the final dose. An additional overfill is included in each vial to ensure that 8 doses (vial of 4 ml) or 10 doses (vial of 5 ml) of 0.5 ml can be delivered. Do not pool excess vaccine from multiple vials. Discard any unused vaccine.

Chemical and physical in-use stability have been demonstrated from the time of vial opening (first needle puncture) to administration for no more than 48 hours in a refrigerator (2°C – 8°C). Within this time period the product may be kept and used at temperatures up to 30°C for a single period of up to 6 hours. After this time period, the product must be discarded. Do not return it to the refrigerator.

Disposal

COVID-19 Vaccine AstraZeneca contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in compliance with the local guidance for genetically modified organisms or biohazardous waste. Spills should be disinfected using agents with activity against adenovirus.

7. MANUFACTURER

SK Bioscience Co Limited (No.97),
150, Saneopdanji-gil, Pungsan-eup,
Andong-si, Gyeongsangbuk-do,
Republic of Korea

8. DATE OF REVISION OF THE TEXT

August 2021
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