Australian Government
Department of Health
Therapeutic Goods Administration

The Managing Director
AstraZeneca Pty Ltd
66 Talavera Road
Macquarie Park NSW 2113

Submission No: PM-2020-06115-1-2
Clinical file: E20-370442
PI/CMI file: E21-223603
Co-ord. file: E20-388235
Quality file: E20-391228
RMP file: E20-381645

Attention: [redacted]
Regulatory Affairs Manager
[redacted]@astrazeneca.com
Regulatory-Affairs-Sydney@astrazeneca.com

Notice of decisions to provisionally register medicine(s), to approve product information, and to impose conditions under the *Therapeutic Goods Act 1989*

Dear Sir/Madam

I refer to your submission dated 27 November 2020 for the provisional registration of COVID-19 Vaccine AstraZeneca (ChAdOx1-S) in the Australian Register of Therapeutic Goods (**ARTG**) under the *Therapeutic Goods Act 1989* (the **Act**). Specifically, your submission relates to the following application:

- AUST R 349072 COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection 5mL multidose vial

This notice comprises the following parts:

Part A: **Decision to provisionally register the medicine(s)**
1. Decision to provisionally register the new biological medicine;
2. Duration and commencement of provisional registration period; and
3. Inclusion of the medicine(s) in the ARTG.

Part B: Decision to approve product information of the medicine(s)
1. Decision to approve; and
2. Lodgement of product information with the TGA.

Part C: Decision to impose conditions

Part D: Other matters

Part A: Decision to provisionally register the medicine(s)

1. Decision to provisionally register

I am a delegate of the Secretary of the Department of Health for the purposes of section 25(3) of the Act. Following the completion of an evaluation of the medicine, I have decided to **provisionally register** the above medicine. My decision is based on the evaluation of the information and data provided with your submission and any subsequent correspondence.

The provisionally approved new indication(s) for the medicine(s) are:

> *"COVID-19 Vaccine AstraZeneca has provisional approval for the indication:*
>
> *Active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.*
>
> *The use of this vaccine should be in accordance with official recommendations.*
>
> *The decision has been made on the basis of short term efficacy and safety data. Continued approval is dependent upon the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment."*

2. Duration and commencement of provisional registration period

The provisional registration period for the above medicine(s) is **two years** starting on the day specified in the ARTG certificate of registration, which will be available for downloading from the eBS Web Site (https://www.ebs.tga.gov.au/) the day following the entry being written to the ARTG.

Note: The above medicine(s) cannot be included in the ARTG until you have provided the TGA with the requisite patent certificate or a notice that such a certificate is not required.

3. Inclusion of medicine(s) in the ARTG

Before the medicine(s) can be included in the ARTG, you are required to either:

- notify the Secretary using the approved form that the patent certification under subsection 26B(1) is not required in relation to the application; OR
- provide a certificate required under subsection 26B(1) of the Act.

The requirement for patent certificates does not apply to applicants for registration of medicines who are not required to submit evidence or information to establish the safety or efficacy of the goods as part of the registration process. In these circumstances, applicants are only required to notify the Secretary in the approved form that the subsection 26B(1) patent certificate is not required in relation to the applications.

The notification form and patent certificate can be downloaded via the TGA website (http://www.tga.gov.au/about/international-usa-fta.htm). You should send the completed and signed notification form or certificate quoting the submission number to the attention of Application Support Team, Medicine Authorisation Branch, TGA, at the address on the footer of this letter. Alternatively, please send a copy by return facsimile message to (02) 6232 8140

or email ast.application.support.team@tga.gov.au. As noted above, a certificate of registration can only be issued after receipt of the completed and signed form or certificate.

Part B: Decision to approve product information for the medicine(s)

1. Decision to approve

I am a delegate of the Secretary of the Department of Health for the purposes of section 25AA(1) of the Act. The text of the product information, provided with your email of 10 February 2021, as set out in the version at **Attachment 1** is approved under subsection 25AA(1) of the Act for these products.

2. Lodgement of product information with the TGA

The product information for the above medicine must be lodged with the TGA **within 2 weeks** of the date of registration of the product.

Further, related Consumer Medicines Information (CMI) document must be lodged with the TGA:

- for new product(s) – prior to supply of the products; or
- for existing product(s) – **within 2 weeks** of the date of registration.

The following statement must be included in the CMI document immediately following the name of the provisionally registered medicine:

> *"This vaccine has provisional approval in Australia to protect people aged 18 years and older against COVID-19 disease. This approval has been granted on the basis of short term safety and efficacy data. Evidence of longer term efficacy and safety from ongoing clinical trials and vaccination in the community continues to be gathered and assessed."*

The documents must be lodged in the TGA eBusiness Services system (eBS). Information on how to lodge these documents is available at www.ebs.tga.gov.au.

Note that documents lodged must be in text PDF format – please be aware that scanned PDF documents will not be accepted by the system.

Part C: Conditions of registration

I am a delegate of the Secretary of the Department of Health for the purposes of subsection 28(2B) of the Act. Under that subsection, I have decided to impose the following conditions in relation to the above medicine(s):

(a) conditions applicable to all registered therapeutic goods as specified in the document Standard Conditions Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989 effective 1 July 1995 (see **Attachment 3**);

(b) With the exception of condition 11, the conditions applicable to specific classes of registered therapeutic goods as specified in the Standard Conditions Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989 effective 1 July 1995 (see **Attachment 3**); and

(c) conditions listed in **Attachment 4 including specific conditions of provisional registration**.

As part of the standard conditions of registration applying to all registered therapeutic goods, it should be noted that, no changes can be made to the goods without the prior approval of the Secretary.

Under paragraph 30(2)(c) of the Act, refusal or failure to comply with a condition of registration to which inclusion of the medicine(s) in the ARTG is subject may result in the suspension or cancellation of registration.

Part D: Other matters

1. The above medicine(s) must conform to the manufacturing and product details provided at **Attachment 2**. These details will be included in the computerised database of the ARTG.

2. **Supply** of the medicine(s) is not permitted until those medicines are formally included in the ARTG.

3. In accordance with regulation 9A of the *Therapeutic Goods Regulations 1990* ("the Regulations"), a patient information document (Consumer Medicines Information - CMI) must be supplied with the goods and be provided to a person to whom the goods are to be administered or otherwise dispensed in such a manner as defined by the subregulation 9A(2). The format of the CMI is set out in Schedule 12 to the Regulations. The CMI submitted with your email of 10 February 2021 is considered to meet the format as set out in Schedule 12.5. There is a continuing obligation to ensure that at all times the CMI complies with the statutory requirements, including consistency with the PI. If the related CMI document needs to be changed as a consequence of the change to the approved PI, it must be lodged with the TGA **within 2 weeks** of the date of the changed PI. In the case of changes relating to the safety or safe use of the product, more rapid change of the CMI may be warranted.

4. With regard to the product labels (international labels referred to as 'EU labels') considered and agreed to for initial supply of the product, please note the following:

   a) The TGA has provided separate decision letters for the following consents/exemptions from Australian-specific labelling requirements for the product:
   - consent for non-compliance with Therapeutic Goods Order No. 91 - Standard for labels of prescription and related medicines (TGO 91); and
   - exemption for absence of the signal heading and cautionary statement, and other general aspects (requirement under the Poisons Standard) (the TGA has also written to State and Territory scheduling bodies alerting them to these exemptions and requesting that any State or Territory that needs to take any action to adopt or endorse such action please do so).

   b) Use of interim labels that do not include an Australian registration number:

   Subsections 19D(3) and (4) of the Act currently provide that the label of a registered therapeutic good supplied in Australia must set out the Australian registration number of the good in the manner prescribed in the Regulations. However, a Bill is

currently before Parliament that proposes to give the Secretary of the Department of Health a discretion to consent to the supply of goods with labels that do not set out the Australian registration number in the prescribed manner.

Subject to the passage of that Bill, it is anticipated that consent will be given, for an interim period, to the supply of COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection 5mL multidose vial with labels that do not include the Australian registration number. Reflecting the spirit of the proposed reform, particularly the public interest in obtaining access to a COVID-19 vaccine as soon as possible, and out of respect for the Parliamentary processes, the TGA will not enforce compliance with subsections 19D(3) and (4) in the event that supply of COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection 5mL multidose vial in Australia commences prior to the anticipated enactment of the Bill and the necessary consent being given. If the Bill is enacted, supply without that consent will be the subject of TGA enforcement action.

Furthermore, as noted above, I have not imposed condition 11 in 'Standard Conditions Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989 effective 1 July 1995', which requires that the registration number of a medicine be placed on the label of a medicine, as a condition of registration.

5. If the product is of biological origin, a permission to import should be requested from:

    Biological Program
    Department of Agriculture
    GPO Box 858
    CANBERRA ACT 2601

    Phone: 02 6272 4578

6. If the medicine contains an active or excipient that is produced by a genetically modified organism, the Office of the Gene Technology Regulator should be informed when supply commences. The address is:

    The Office of the Gene Technology Regulator
    GPO Box 9848
    Canberra ACT 2601

7. The National Director of Pharmaceutical Services, Department of Veterans' Affairs, would like to be provided with a copy of the approved PI for this product. Please consider providing a copy to:

    National Director of Pharmaceutical Services
    Department of Veterans' Affairs
    GPO Box 9998
    In Your Capital City

Request for reconsideration of an initial decision
This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister within 90 days and be accompanied by any information that you wish to have considered. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate to an officer of the Department with the appropriate delegation. Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the notification is made of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

3. Guidelines for requesting reconsideration of an initial decision

A request for reconsideration should be made in writing, signed and dated by the person requesting reconsideration, should be titled **"<insert person/company name> - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989***" and should include the following:

- a copy of the initial decision notification letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: '**minister.hunt.DLO@health.gov.au**' and copied to '**decision.review@health.gov.au**'

Requests for reconsideration that include dossiers (or similar bulk material) that cannot easily be attached to the request given first by email, may then be submitted on a USB drive or CD sent by express post or registered mail to:

Mail: **Minister for Health**
Suite M1 40
c/- Parliament House
CANBERRA ACT 2600

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

Yours sincerely,

Signed and authorised by
[redacted]
Delegate of the Secretary
Clinical Evaluation Section A
Prescription Medicines Authorisation Branch
Email: [redacted]@health.gov.au

15 February 2021

Attachments

1. Approved product information.

2. Manufacturing and Product Details to which the Goods Must Conform.

3. Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989.

4. Specific Conditions Applying to these Therapeutic Goods.

5. EU Anangi Carton label

6. EU Anangi Vial label

7. EU Catalent Stickers

▼This vaccine is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection

1 NAME OF THE MEDICINE

ChAdOx1-S (provisional ABN)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each multi-dose vial contains $5x10^{11}$ viral particles (vp) of (ChAdOx1-S [a, b]) in 5 mL.

One dose (0.5 mL) contains $5x10^{10}$ vp of (ChAdOx1-S [a, b]).

[a] Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein (GP)

[b] The vaccine is manufactured using material originally sourced from a human embryo (Human Embryonic Kidney cells: HEK293)

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opaque, colourless to slightly brown, particle free with a pH of 6.1 – 7.1.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

COVID-19 Vaccine AstraZeneca has **provisional approval** for the indication:

Active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

The use of this vaccine should be in accordance with official recommendations.

The decision has been made on the basis of short term efficacy and safety data. Continued approval is dependent upon the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.

4.2 DOSE AND METHOD OF ADMINISTRATION

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 (see Section 5.1 Pharmacodynamic properties).

It is recommended that individuals who receive a first dose of COVID-19 Vaccine AstraZeneca complete the vaccination course with COVID-19 Vaccine AstraZeneca (see Section 4.4 Special warnings and precautions for use).

Special patient populations

Use in the elderly

No dosage adjustment is required in elderly individuals ≥65 years of age (see Section 4.4 Special warnings and precautions for use).

Paediatric use

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

Method of administration

COVID-19 Vaccine AstraZeneca is for intramuscular (IM) injection only, preferably in the deltoid muscle.

To facilitate the traceability of the vaccine, the name and the batch number of the administered product should be clearly recorded for each recipient.

COVID-19 Vaccine AstraZeneca 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. Do not shake.

Each vaccine dose of 0.5 mL is withdrawn into a syringe for injection to be administered intramuscularly. 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 (2ºC to 8ºC).

The vial can be re-refrigerated, but after first opening 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.

The vials, needles, syringes should be disposed of in the clinical waste bin (see Section 6.6 Special precautions for disposal).

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with any vaccine, vaccination with COVID-19 Vaccine AstraZeneca may not protect all vaccine recipients. Vaccination does not mitigate the need to follow other official recommendations to prevent the spread of COVID-19

Hypersensitivity

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.

Concurrent illness

As with other vaccines, administration of COVID-19 Vaccine AstraZeneca should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, COVID-19 Vaccine AstraZeneca 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.

Neurological events

Very rare events of demyelinating disorders have been reported following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established.

As with other vaccines, the benefits and potential risks of vaccinating individuals with COVID-19 Vaccine AstraZeneca should be considered.

Immunocompromised individuals

The immunogenicity, efficacy and safety of COVID-19 Vaccine AstraZeneca has not been assessed in immunocompromised individuals, including those receiving immunosuppressive therapy. The immunogenicity of vaccines may be lower in immunosuppressed patients.

Duration of protection

The duration of protection has not yet been established. Studies are ongoing.

Interchangeability

There are no safety, immunogenicity or efficacy data to support interchangeability of COVID-19 Vaccine AstraZeneca with other COVID-19 vaccines.

Use in the elderly

There are currently limited data available for the efficacy and safety in individuals over 65 years of age. Further information will be collected from ongoing clinical studies and post-market monitoring. The decision to immunise an elderly patient should be decided on a case-by-case basis with consideration of age, co-morbidities, their environment, potential benefits and potential risks.

Use in individuals with significant co-morbidities

There are currently limited data available for the efficacy and safety in individuals with significant co-morbidities. The decision to immunise an individual should be made on the basis of potential benefits over risks to that individual.

Paediatric use

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

Effects on laboratory tests

Vaccination with COVID-19 Vaccine AstraZeneca leads to the development of antibodies to the SARS-CoV-2 S protein. This does not interfere with results from SARS-CoV-2 PCR testing.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The safety, immunogenicity and efficacy of co-administration of COVID-19 Vaccine AstraZeneca with other vaccines have not been evaluated.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy – Category B2

There are a limited amount of data from the use of COVID-19 Vaccine AstraZeneca in pregnant women, or women who became pregnant after receiving the vaccine. The data are insufficient to inform on vaccine associated risk.

Animal reproductive toxicity studies have not been completed.

As a precautionary measure, vaccination with COVID-19 Vaccine AstraZeneca is not recommended during pregnancy. Use of COVID-19 Vaccine AstraZeneca in pregnant women should be based on an assessment of whether the benefits of vaccination outweigh the potential risks.

Use in lactation

There are no or limited data from the use of COVID-19 Vaccine AstraZeneca in lactating women. A risk to breastfed newborns/infants cannot be excluded.

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 Adverse effects (Undesirable effects) may temporarily affect the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

Overall 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.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 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.

The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). 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.

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

Analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used to provide symptomatic relief from post-vaccination adverse reactions.

Safety in subgroups including the frail elderly, immunosuppressed, and pregnancy is unknown due to the low number of representative participants from these groups. Further information will become available from ongoing clinical studies and pharmacovigilance programmes.

Adverse drug reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. 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).

Table 1 Adverse Drug Reactions (ADR) – pooled data set (safety analysis set[a])

MedDRA SOC	Adverse reaction[b]	COVID-19 Vaccine AstraZeneca (N= 10, 069)	Control[c] (N= 9, 902)
Nervous system disorders	Headache	Very common (52.6%)	Very common (39.0%)
Gastrointestinal disorders	Nausea	Very common (21.9%)	Very common (13.1%)
Musculoskeletal and connective tissue disorders	Muscle pain (Myalgia)	Very common (44.0%)	Very common (21.6%)
	Joint pain (Arthralgia)	Very common (26.4%)	Very common (12.4%)
General disorders and administration site conditions	**Local**		
	Injection site tenderness	Very common (63.7%)	Very common (39.5%)
	Injection site pain	Very common (54.2%)	Very common (36.7%)
	Injection site warmth	Very common (17.7%)	Very common (14.5%)
	Injection site itch (Injection site pruritus)	Very common (12.7%)	Common (7.5%)
	Injection site swelling	Common (3.4%)	Common (1.6%)
	Injection site redness (Injection site erythema)	Common (3.1%)	Common (1.4%)
	Systemic		
	Fatigue	Very common (53.1%)	Very common (38.2%)
	Malaise	Very common (44.2%)	Very common (20.2%)
	Feverishness[d] (Pyrexia)	Very common (33.6%)	Very common (10.7%)

MedDRA SOC	Adverse reaction[b]	COVID-19 Vaccine AstraZeneca (N= 10, 069)	Control[c] (N= 9, 902)
	Chills	Very common (31.9%)	Common (8.3%)
	Fever[d] (Pyrexia)	Common (7.9%)	Common (1.2%)

[a] Frequencies of ADRs are reported from the safety analysis set where participants received the recommended dose (5×10^{10} vp) as their first dose.

[b] Solicited event reporting terms, where applicable MedDRA preferred terms are given in parentheses

[c] Control was either meningococcal vaccine or saline solution

[d] Defined as: Feverishness, (subjective) a self-reported feeling of having a fever; Fever, (objective) ≥38°C

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Clinical trials

This section will be updated as evidence emerges from ongoing clinical studies.

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

The efficacy and safety of COVID-19 Vaccine AstraZeneca has been evaluated based on an interim analysis (data lock: 4 November 2020) of pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001 (NCT04324606), in healthy adults 18 to 55 years of age in the UK; a Phase II/III Study, COV002 (NCT04400838), in adults ≥18 years of age (including the elderly) in the UK; a Phase III Study, COV003 (ISRCTN89951424), in adults ≥18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV005 (NCT04444674), in adults aged 18 to 65 years of age in South Africa. 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. In studies COV001 and COV002, licensed seasonal influenza and pneumococcal vaccinations were permitted (at least

7 days before or after their study vaccine). All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease. These studies are ongoing.

The interim efficacy analysis was based upon the results of COV002 and COV003, as at that time studies COV001 and COV005 had <5 virologically confirmed COVID-19 cases per study and therefore did not meet the predefined statistical threshold to be included in the efficacy analysis.

In the pooled analysis for efficacy (COV002 and COV003), participants ≥18 years of age received two doses of COVID-19 Vaccine AstraZeneca (N=5,807) or control (meningococcal vaccine or saline) (N=5,829). Participants randomised to COVID-19 Vaccine AstraZeneca received either two standard doses [SD] (5×10^{10} vp per dose) or one low dose [LD] (2.2×10^{10} vp) followed by one SD (5×10^{10}vp), administered via IM injection.

Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 4 to 26 weeks.

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, 94.1% of participants were 18 to 64 years old (with 5.9% aged 65 or older); 60.7% of subjects were female; 82.8% were White, 4.6% were Asian, and 4.4% were Black. A total of 2,070 (35.6%) participants had at least one pre-existing mild comorbidity (defined as a BMI ≥30 Kg/m^2, cardiovascular disorder, respiratory disease or diabetes). At the time of interim analysis the median follow up time post-dose 1 was 4.7 months and post-dose 2 was 2.2 months.

The primary efficacy endpoint was symptomatic COVID-19 infection, defined as objective fever (≥37.8°C), cough, shortness of breath, anosmia, or ageusia with virologically confirmed COVID-19 occurring ≥15 days post second dose, in participants without serological evidence of previous SARS-CoV-2 infection. 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 131 participants met the primary efficacy endpoint criteria. 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

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95.84% CI)
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Primary analysis population					
Participants who had 2 doses of COVID-19 AstraZeneca & were seronegative at baseline & followed ≥15 days after the 2nd dose [a]	5807	30 (0.52)	5829	101 (1.73)	70.42 (54.84, 80.63)
Licensing regimen					
Participants who had 2 doses of the standard dose & were followed for ≥15 days after the 2nd dose.	4440	27 (0.61)	4455	71 (1.59)	62.10 (39.96, 76.08)

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

[a] some of the participants in this group received an initial LD. These were included in the primary analysis as the immune response in this group was similar to that in the SD and efficacy would therefore be expected to be the same. However, when this subgroup was analysed, the efficacy was greater. There are many factors other than having a LD that may have influenced the results (including lower age, longer duration between doses), thus the use of a LD will not be considered further for regulatory purposes. Two doses of vaccine are required.

The level of protection gained from a single dose of COVID-19 Vaccine AstraZeneca was assessed in an exploratory analysis that included participants who had received one dose. Participants were censored from the analysis at the earliest time point of when they received a second dose or at 12 weeks post-dose 1. In this population, vaccine efficacy from 22 days post-dose 1 was 73.00% (95% CI: 48.79; 85.76 [COVID-19 Vaccine AstraZeneca 12/7,998 vs control 44/7,982]).

An exploratory analyses of the impact of duration between doses and efficacy demonstrated greater efficacy with increasing duration between vaccine doses (Table 3). This was supported by the immunogenicity data (see Immunogenicity Table 4).

Table 3 Vaccine efficacy for incidence of first SARS-CoV-2 virologically confirmed symptomatic COVID-19 occurring ≥15 days post second dose by dose interval (SDSD seronegative for efficacy analysis set)

Dose interval	Participants with events, n (%)				Vaccine efficacy (%)	95% CI (%)
	N	COVID-19 Vaccine AstraZeneca n (%)	N	Control n (%)		
< 6 weeks	1702	9 (0.53)	1698	19 (1.12)	53.28	(-3.21, 78.86)
6–8 weeks	562	5 (0.88)	521	9 (1.73)	51.08	(-45.57, 83.56)
9–11 weeks	1056	9 (0.85)	1110	24 (2.16)	60.55	(15.23, 81.64)
≥12 weeks	1120	4 (0.36)	1126	19 (1.69)	78.79	(37.63, 92.79)

Vaccine efficacy (VE) of COVID-19 Vaccine AstraZeneca versus control, the 95% CI and p value were estimated based on Poisson regression with robust variance including the term of treatment as well as the log of the follow-up time as an offset.

VE is defined as 1-(incidence from the COVID-19 Vaccine AstraZeneca arm / incidence from the control arm) expressed as a percentage, where the risk ratio is derived from Poisson regression with robust variance. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio derived from the model.

The observation period for the endpoint was 15 days post second dose up to 1 year in study.

COVID-19 endpoints were based on adjudicated events.

COVID-19 Vaccine AstraZeneca reduced COVID-19 hospitalisation (WHO Severity grading ≥4). In all participants who received SD as a first dose, as from 22 days post dose 1, there were 0 (0.0%, N=6,307) cases of COVID-19 hospitalisation in participants who received COVID-19 Vaccine AstraZeneca (N=6,307), as compared to 9 (0.14%, N=6,297) reported for control.

Participants who had one or more mild comorbidities had a vaccine efficacy of 73.43% [95% CI: 48.49; 86.29]; 11 (0.53%) vs 43 (2.02%) for COVID-19 Vaccine AstraZeneca (N=2,070) and control (N=2,113), respectively; which was similar to the vaccine efficacy observed in the overall population.

The number of COVID-19 cases in the subgroup of participants ≥65 years old were too few to draw conclusions on efficacy. In this sub-population, efficacy has been inferred from immunogenicity data and efficacy demonstrated in the general population.

Limited data are available on the impact of emerging SARS-CoV-2 variants of concern on vaccine efficacy. Further information will be collected throughout the AZD1222 clinical development program by clinical and surveillance virology monitoring.

Immunogenicity

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

An immunological correlate of protection has not been established; therefore the level of immune response that provides protection against COVID-19 is unknown.

Following vaccination with COVID-19 Vaccine AstraZeneca, in participants who were seronegative at baseline, seroconversion (as measured by a ≥4 fold increase from baseline in S-binding antibodies) was demonstrated in ≥98% of participants at 28 days after the first dose and >99% at 28 days after the second. Higher S-binding antibodies were observed with increasing dose interval (see Table 4).

Generally similar trends were observed between analyses of neutralising antibodies and S-binding antibodies.

Table 4 SARS-CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca (SDSD)[a]

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	**GMT (95% CI)**	**GMT (95% CI)**
Overall	(N=882) 57.18 (52.8, 62.0)	(N=817) 8386.46 (7758.6, 9065.1)	(N=819) 29034.74 (27118.2, 31086.7)
Dose Interval			
<6 weeks	(N=481) 60.51 (54.1, 67.7)	(N=479) 8734.08 (7883.1, 9676.9)	(N=443) 22222.73 (20360.50, 24255.3)
6-8 weeks	(N=137) 58.02 (46.3, 72.6)	(N=99) 7295.54 (5857.4, 9086.7)	(N=116) 24363.10 (20088.5, 29547.3)
9-11 weeks	(N=110) 48.79 (39.6, 60.1)	(N=87) 7492.98 (5885.1, 9540.2)	(N=106) 34754.10 (30287.2, 39879.8)
≥12 weeks	(N=154) 52.98 (44.4, 63.2)	(N=152) 8618.17 (7195.4, 10322.3)	(N=154) 63181.59 (55180.1, 72343.4)

N = Number of subjects included in each group; GMT = Geometric mean titre; CI = Confidence interval; S = Spike

[a] Immune response evaluated using a multiplex immunoassay

The immune response observed in participants with one or more comorbidities was consistent with the overall population.

High seroconversion rates were observed in older adults (≥65 years) after the first SD (97.8% [N=136, 95% CI: 93.7; 99.5]) and the second SD (100.0% [N=111, 95% CI: 96.7; NE]). The increase in S-binding antibodies was numerically lower for participants ≥65 years old (28 days after second SD: Geometric mean titre (GMT)=20,727.02 [N=116, 95% CI: 17,646.6; 24,345.2]) when compared to participants aged 18-64 years (28 days after second SD: GMT=30,695.30 [N=703, 95% CI: 28,496.2; 33,064.1]). The majority of participants ≥65 years old had a dose interval of <6 weeks, which may have contributed to the numerically lower titres observed.

In participants with serological evidence of prior SARS-CoV-2 infection at baseline (GMT=13,137.97 [N=29; 95% CI: 7,441.8; 23,194.1]), S-antibody titres peaked 28 days after dose 1 (GMT=175,120.84 [N=28; 95% CI: 120,096.9; 255,354.8).

Spike-specific T-cell responses as measured by IFN-ɣ enzyme-linked immunospot (ELISpot) assay are induced 14 days after a first dose of COVID-19 Vaccine AstraZeneca. These do not rise further after a second dose.

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Toxicity and local tolerance studies

Non-clinical data obtained from toxicology and local tolerance studies with investigational vaccines utilising the same ChAdOx1 adenoviral vector vaccine technology as COVID-19 Vaccine AstraZeneca, concluded that the ChAdOx1 technology was well tolerated in mice and was not associated with any adverse effects.

Genotoxicity

COVID-19 Vaccine AstraZeneca is a vaccine, as such, genotoxicity (mutagenicity) studies have not been conducted.

Carcinogenicity

COVID-19 Vaccine AstraZeneca is a vaccine, as such, carcinogenicity studies have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

COVID-19 Vaccine AstraZeneca contains the excipients histidine, histidine hydrochloride monohydrate, sodium chloride, magnesium chloride hexahydrate, disodium edetate (EDTA), sucrose, ethanol absolute, polysorbate 80 and water for injections.

COVID-19 Vaccine AstraZeneca does not contain any preservatives and the vial stopper is not made with natural rubber latex.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened multidose vial

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Store in outer carton in order to protect from light.

Opened multidose vial

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 30°C, or
- 48 hours in a refrigerator (2°C to 8°C)

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

6.5 NATURE AND CONTENTS OF CONTAINER

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

6.6 SPECIAL PRECAUTIONS FOR 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 in a clinical waste bin. Spills should be disinfected with an appropriate antiviral disinfectant.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

2420395-83-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

For COVID-19 Vaccine AstraZeneca enquiries contact 1800 343 949 or visit azcovid-19.com

9 DATE OF FIRST APPROVAL

<<draft 10 February 2021>>

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	New product

Doc ID-004452129 v4 (clean version of annotated PI Doc ID-004370127 v6)

Attachment 2.

PROVISIONAL ARTG RECORD

Label Name:	COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection 5mL multidose vial	**Provisional ARTG Number:**	349072
Sponsor:	AstraZeneca Pty Ltd	**Sponsor ID:**	39

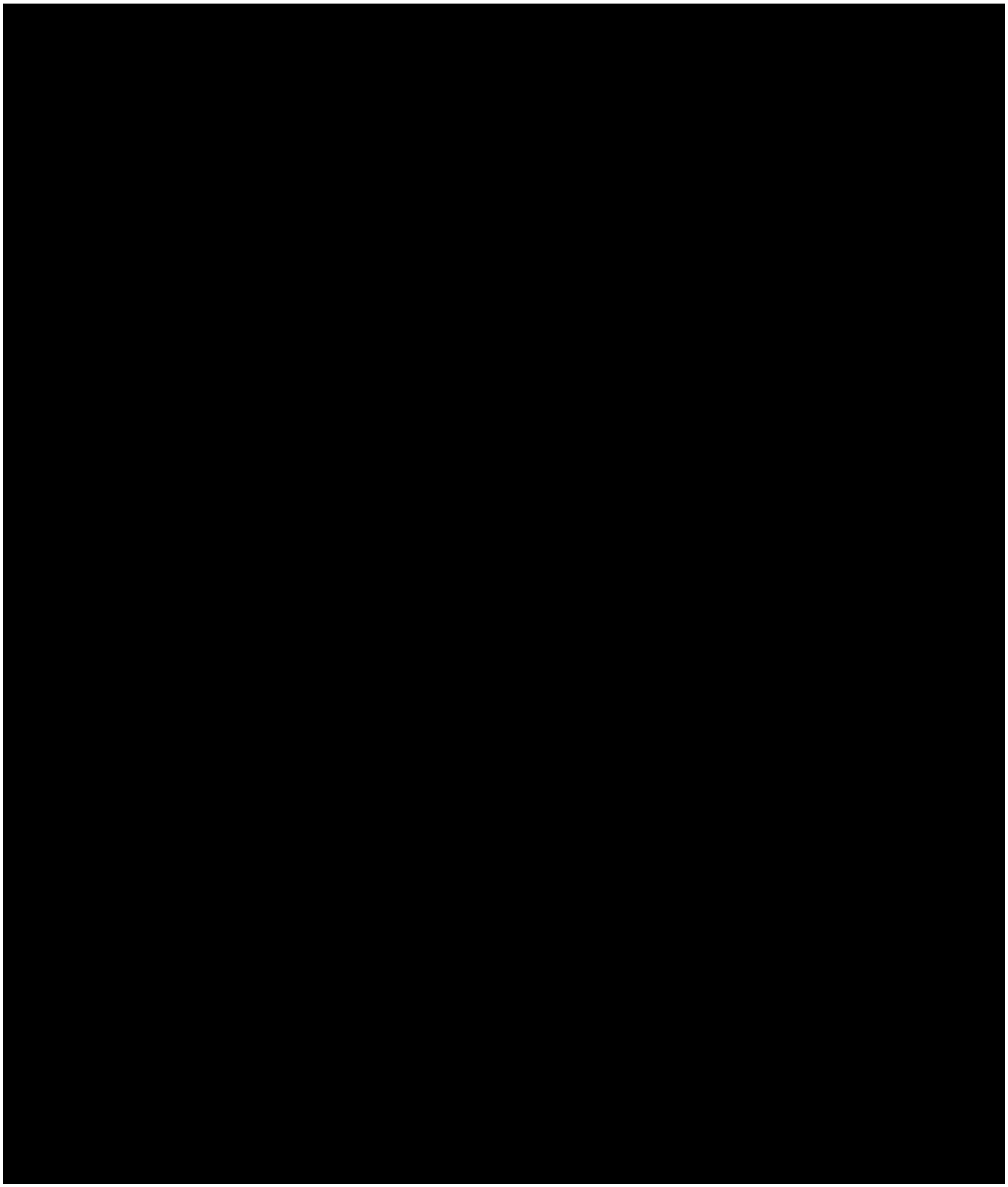
Approval Area: Drug Safety Evaluation Branch
RegistrationType: Registered (Provisional)
Provisional Registration Lapse Date:
Black Triangle Scheme Indicator: Yes
Black Triangle Scheme Lapse Date:
Charge Level: Registered Biologics Annual Charge

Standard Conditions of Approval:

Conditions applicable to all therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

Conditions applicable to the relevant category and class of therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

[redacted]



PRODUCT DETAILS

Product Name: COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection 5mL multidose vial
Product ID: 751237
Product Status:

Product Type: Single Medicine Product

Grouping: No

Supplied In Australia:

ATC: Vaccines

Medicine Product Information: Primary Pack Label
Container Label

Non-standard Indications:

Indication	Provisionally Registered
COVID-19 Vaccine AstraZeneca has provisional approval for the indication: Active immunisation of individuals 18 years old for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. The use of this vaccine should be in accordance with official recommendations. The decision has been made on the basis of short term efficacy and safety data. Continued approval is dependent upon the evidence of longer-term efficacy and safety from ongoing clinical trials and post-market assessment.	Yes

Pack Size
5mL (10 x 0.5mL) vial - 10 vials per pack

Poison Schedule
(S4) Prescription Only Medicine

PRODUCT CONTAINER

Material	Closure	Container Condition	Time	Temperature	Condition
Glass Type I Clear	Neither child resistant closure nor restricted flow insert	Closed	6 Months	Store at 2 to 8 degrees Celsius	Do not Freeze Do not Shake Store in Original Container Protect from Light

Container Type: Vial

PRODUCT STERILITY

Part	Text	Method
	solution for injection	Filtration
	solution for injection	Aseptic Handling

COMPONENT DETAILS

Product Name: COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection 5mL multidose vial
Product ID: 751237

Component: COVID-19 Vaccine AstraZeneca (ChAdOx1-S) solution for injection 5mL multidose vial
Component ID: 646452

Dosage Form:	Injection, solution
Route of Administration:	Intramuscular
Visual Identification:	Clear to slightly opaque, colourless to slightly brown, particle free solution in clear glass vial, elastomeric stopper & aluminium overseal

COMPONENT FORMULATION

Active Ingredients	[redacted]
ChAdOx1-S	
Excipient Ingredients	
histidine	
magnesium chloride hexahydrate	
sucrose	
disodium edetate	
polysorbate 80	
sodium chloride	
histidine hydrochloride monohydrate	
ethanol absolute	
water for injections	

Australian Government
Department of Health
Therapeutic Goods Administration

Attachment 3

STANDARD CONDITIONS

Applying to registered or listed therapeutic goods under Section 28 of the *Therapeutic Goods Act 1989* (*Effective 1 July 1995*)

For the purposes of these conditions, words used in any of the paragraphs set out below shall have the same meaning as their counterparts in the *Therapeutic Goods Act 1989*. Unless otherwise specified, references to the 'Act' shall be a reference to the *Therapeutic Goods Act 1989*, as amended from time to time, and references to the 'Regulations' shall be to the Therapeutic Goods Regulations as amended from time to time. A reference to 'registered goods' or 'listed goods' shall be a reference to the goods included in the Certificate of Registration or the Certificate of Listing, as the case may be.

APPLYING TO ALL REGISTERED OR LISTED THERAPEUTIC GOODS

1 Standards
The registered/listed goods must comply with standards applicable to those goods under part 2 of the Act;

2 Changes to Goods
Changes or variations in respect of any information concerning the registered or listed therapeutic goods, being information that would have been relevant* to a decision to register/list the goods in the Register, including information on the formulation of the registered/listed goods or other aspects of their manufacture, and the labelling of the goods, shall forthwith be notified to the Secretary, or the Secretary's delegate appointed for the purposes of section 28 of the Act, and where necessary*, the change or variation shall not be implemented until approved by the Secretary. (*Reference should also be made to Appendix *Changes to Therapeutic Goods)*

3 Australian Manufacturers
The Australian manufacturer or manufacturers of the registered/listed goods, and any subcontractor or testing facilities in Australia contracted to, or otherwise engaged to, manufacture the registered/listed goods, must be appropriately licensed to carry out the manufacture, or a step in the manufacture, of the goods or the class of therapeutic goods within which the registered/listed goods are included, unless otherwise exempted under the Act from the need to comply with such a requirement.

4 Records Held
The sponsor of the registered/listed goods shall keep such records relating to the goods as are necessary:

(a) to expedite recall if necessary of any batch of the registered/listed goods;
(b) to identify the manufacturer(s) of each batch of the registered/listed goods.

Where any part of or step in the manufacture in Australia of the registered/listed goods is sub-contracted to a third party who is not the sponsor, copies of relevant Good Manufacturing Practice agreements relating to such manufacture shall be kept.

5

Each sponsor shall retain records of the distribution of all of the sponsor's registered/listed goods for a period of five years and upon the request of the National Manager, Therapeutic Goods Administration, shall provide the records or copies of the records to the National Manager.

6 Sampling

The sponsor of the registered/listed goods shall permit officers who have been authorised under the Regulations to do so to take samples of therapeutic goods and carry out related duties in accordance with the Regulations.

7 Overseas Regulatory Actions

Where the registered/listed goods are distributed regularly overseas as well as in Australia, product recall or any actions other similar regulatory action taken in relation to the goods outside Australia which has or may have relevance to the quality, safety or efficacy of the goods distributed in Australia must be notified to the National Manager, Therapeutic Goods Administration immediately the action or information is known to the sponsor.

8 Date of Supply

The sponsor of the registered/listed goods shall advise the National Manager, Therapeutic Goods Administration (through the Operations Manager, Australian Register of Therapeutic Goods) of the date of initial supply of those goods.

LISTED THERAPEUTIC GOODS

9 Indications

In relation to listed goods, the sponsor must have and shall retain, while the goods remain listed, evidence necessary to substantiate and support the accuracy of the indications in relation to the listed goods and, upon the request of the Director, Chemicals & Non Prescription Drug Branch, or Director, Conformity Assessment Branch, Therapeutic Goods Administration, shall produce such evidence to the Director.

CONDITIONS APPLYING TO ALL REGISTERED OR LISTED DRUGS

10 Labels (see also condition 2)

A copy[1] of the label or, if more than one label, labels to be used in respect of the registered/listed drugs shall be provided to the National Manager, Therapeutic Goods Administration (through the Operations Manager, Australian Register of Therapeutic Goods), upon:

(a) the commencement of the supply of the registered/listed drugs; and
(b) request by the National Manager.

1 Where practicable actual labels should be provided attached to a sheet of paper which identifies the product by its Registration/Listing Name and Number. Photocopies (actual size) are acceptable where the label information is printed or embossed directly onto the container.

11 Registration/Listing Number

The registration or listing number shall be placed on the label of the registered/listed drugs in accordance with the requirements of the Therapeutic Goods Act 1989 and in the manner prescribed in the Regulations.

12 Expiry dates

The sponsor shall not supply the registered/listed drugs after the expiry date of the goods.

13 Colouring

Colouring agents used in registered/listed drugs for ingestion, other agents than those listed for export only, shall be only those included in the list of "Colourings for Use in Pharmaceuticals for Ingestion" issued by the National Health and Medical Research Council in November 1988 as amended from time to time.

14 Adverse reactions

All reports of adverse reactions or similar experiences associated with the use or administration of the registered/listed drugs shall be notified to the National Manager, Therapeutic Goods Administration, as soon as practicable after the sponsor of the goods becomes aware of those reports. Sponsors of drugs must retain records of such reports for a period of not less than 18 months from the day the National Manager is notified of the report or reports. It is a condition of registration that your company must comply with Appendix 20 of Volume 1 of the Australian Guidelines for the Registration of Drugs. That appendix deals with the reporting of adverse drug reactions.

CONDITIONS APPLYING TO ALL REGISTERED DRUGS

15 Authorised Officer

It is a condition of registration that as the sponsor of this product you will comply with Regulation 24 of the Therapeutic Goods Regulations.

16 Overseas Regulatory Action

It is a condition of registration that your company must inform the TGA if an application is rejected in the USA or Canada at any time during or after registration in Australia and must submit detailed reasons for the rejection.

REGISTERED OR LISTED THERAPEUTIC DEVICES

17 Problems with Therapeutic Devices

The sponsor of registered/listed therapeutic devices shall:

(a) keep a log of problems relating to the condition, use or application of the registered/listed therapeutic devices,

(b) as soon as possible after the sponsor becomes aware of it, report to the Director, Conformity Assessment Branch, TGA, all deaths, serious illness and serious injuries arising from or attributable in some way to, the use or application of the registered/listed therapeutic devices.

REGISTERED THERAPEUTIC DEVICES

18 Registration Number

The registration number shall be placed on the label of the registered therapeutic devices in accordance with the requirements of the *Therapeutic Goods Act 1989* and in the manner prescribed in the Regulations.

19 Reports of Problems

The sponsor shall provide to the Director, Conformity Assessment Branch, Therapeutic Goods Administration:

(a) a summarised report in respect of problems relating to the condition, use or application of the registered therapeutic devices between 1 July and 1 October following the date of the registration of the registered therapeutic devices,

(b) and then submit annual summarised reports between 1 July and 1 October for the following three years.

REGISTERED AND LISTED THERAPEUTIC DEVICES SPECIFIED UNDER REGULATION 16 (SCHEDULE 6)

20 Labels (see also condition 2)

A copy[1] of the label or, if more than one label, labels to be used in respect of the registered/listed goods shall be provided to the National Manager, Therapeutic Goods Administration (through the Operations Manager, Australian Register of Therapeutic Goods), upon:

(a) the commencement of the supply of the registered/listed goods; and

(b) request by the National Manager.

[1] Where practicable actual labels should be provided attached to a sheet of paper which identifies the product by its Registration/Listing Name and Number. Photocopies (actual size) are acceptable where the label information is printed or embossed directly onto the container.

CONDITIONS APPLYING TO SPECIFIC CLASSES OF THERAPEUTIC GOODS

21 Conditions Applying to Drugs Which Include Bioflavonoids

Bioflavonoids shall comply with the monograph developed by the Nutritional Foods Association and the Therapeutic Goods Administration.

22 Conditions Applying to Drugs Which Contain Substances Which Are "Drugs of Dependence"

Where the registered or listed goods contain a substance which is included in the Fourth Schedule to the Customs (Prohibited Imports) Regulations or the Eighth Schedule to the Customs (Prohibited Exports) Regulations the Sponsor shall, at the time of importation or exportation of the goods, be in possession of a licence and a permission for importation or exportation of each consignment of the goods as required by those regulations.

23 Goods Manufactured Overseas

Where the registered/listed goods are imported goods which if manufactured in Australia would be required under the provisions of the Act to be manufactured in licensed premises, the sponsor of the goods shall, upon request at any time by the Secretary or the Secretary's delegate appointed for the purposes of section 31 of the Act, provide to the National Manager, Therapeutic Goods Administration, an acceptable form of evidence which establishes the standard of manufacture of the goods. If this is not available, the sponsor shall pay the costs of an inspection of the principal manufacturer of the goods by Australian inspectors where

this is considered necessary by the Secretary or the Secretary's delegate referred to in this paragraph.

Specific Conditions

on Registration or Listing applying to specific groups of therapeutic devices under Section 28 of the *Therapeutic Goods Act 1989*

EFFECTIVE 1 MARCH 1998

	Product Type	Applicable Therapeutic Goods Orders	Additional Conditions
1	Bandages, dressings and allied products supplied non-sterile		For non GMP approved manufacturers, total microbial count certificates, must be provided [3] for the subsequent five batches of product supplied following listing of the product.
1.1	Primary dressings, surgical absorbents or goods specified in Schedule 11 of the Regulations	TGO 11 - 'Standard for Sterile Therapeutic Goods'	Must be sterile and labelled "sterile"
2.	Barium hydroxide lime	TGO 47 - 'Barium Lime'	Test certificate on request[1]
3	Catheters (Urethral)	TGO 59 - 'Polymer Urethral Catheters for General Medical Use'	Test certificate on request[1]
4	Condoms	TGO 61 - 'Contraceptive Devices - Rubber Condoms'	Test certificate must be obtained for every batch prior to supply
5	Contrast media injectors (powered)		Annual problem reports to be lodged with CAB[2]
6	Dental restorative materials	TGO 57 - 'Standard for Dental Materials'	Test certificate on request[1]
7	Diaphragms (Contraceptive)	TGO 28 - 'Standard for Contraceptive Devices - Diaphragms'	Test certificate must be obtained for every batch prior to supply
8.	Disinfectants & Sterilants	TGO 54 - 'Standard for Composition, Packaging, Labelling and Performance of Disinfectants and Sterilants' TGO 54A -Amendment to TGO54	Test certificate on request[1]
9	Gloves - examination	TGO 52 - 'Gloves for general medical and dental use'	Test certificate on request[1]
9.1	Gloves - surgical	TGO 53 - 'Single Use , Sterile (Surgical) Rubber Gloves'	Test certificate on request[1]
10	Implantable patient activated drug delivery systems		Annual problem reports to be lodged with CAB[2]

	Product Type	Applicable Therapeutic Goods Orders	Additional Conditions
11	In Vitro Diagnostics [IVDs] containing material of human origin	TGO 34 - 'Standard for Diagnostic Goods of Human Origin'	Test certificate on request[1] Current catalogues and detailed records of importation and distribution of the goods must be kept by the sponsor.
11.1	In Vitro Diagnostics [IVDs] approved for use as screening or as supplemental tests for the diagnosis of infection with Human Immunodeficiency Virus [HIV] (viral load assays excepted).		May be supplied to authorised laboratories only
11.2	In Vitro Diagnostics [IVDs] approved as supplemental tests for the diagnosis of infection with Hepatitis C Virus [HCV]		May be supplied to authorised laboratories only
11.3	In Vitro Diagnostics [IVDs] for home use or supplied as a Commonwealth Pharmaceutical Benefit under the *National Health Act 1953* or the *Veterans' Entitlement Act 1986*		Must be accompanied by adequate instructions and information in plain English which outlines clearly the nature, use and limitations of the test and expresses measurements in Standard International units
12	Insulin syringes	TGO 41 - 'Single-use syringes (sterile) for the injection of 100 units per millilitre of insulin (U-100)'	Test certificate on request[1]
13	Menstrual tampons	TGO 51 - 'Standard for Tampons - Menstrual'	Test certificate on request[1]
14	Penile implants - inflatable		Annual problem reports to be lodged with CAB[2]
15	Pyrogen free - products presented as being such, and all devices specified in the Order	TGO 50 - 'General Standard for Pyrogen and Endotoxin Content of Therapeutic Goods'	Test certificate on request[1]
16	Silicone gel - devices containing (breast implants excepted)		Annual problem reports to be lodged with CAB[2]
17	Sutures or ligatures	TGO 49 - 'General Standard for Sutures'	Test certificate on request[1]

[1] **Test certificate on request** - the sponsor of the goods must obtain a test certificate, consisting of a detailed certificate of compliance containing comments against each requirement of the Order, for each batch of goods prior to supply in Australia. These certificates must be held by the sponsor and must be available whenever the Secretary or a delegate of the Secretary appointed for the purposes of Section 28 of the Act, should request it to be produced for inspection.
[2] **Annual problem reports** - a report of problems relating to the condition, use or application of the devices must be submitted to the Director, Conformity Assessment Branch between 1 July and 1 October each year.
[3] **Microbial count certificates** relating to non-sterile bandages, dressings and allied products must be submitted to the Senior Technical Reviewer, Conformity Assessment Branch.

For further information contact the TGA Publications Office on 1 800 020 653

Attachment 4

SPECIFIC CONDITIONS APPLYING TO THESE THERAPEUTIC GOODS

1. All of the manufacturing and product details as described in Attachment 2 apply to these therapeutic goods.

2. The Product Information applying to these therapeutic goods must meet the TGA's approval at all times. Any proposed changes to the approved text of the PI, including safety related changes, must be submitted to, and be approved by, the TGA prior to distribution.

3. Abridged Product Information must accurately reflect the approved Product Information, including safety-related statements, but may be a paraphrase or précis of the approved Product Information.

4. Appropriate quantities of the reference material for the active ingredient, as well as of precursors, degradation products and other impurities for which limits are set in the finished product specifications are to be provided free of charge to the TGA, if required for testing purposes.

5. Promotional material (other than Product Information) relating to the registered good must comply with the requirements of the Code of Conduct of Medicines Australia.

6. You must supply a copy of any or all current labels for these products within two working days of a request from the TGA. Please note that this condition replaces Condition No. 10 of the Standard Conditions Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989 (Effective 1 July 1995).

Clinical

7. The sponsor is to provide the full study reports of studies COV001, COV002, COV003 and COV005 when available in 2022 as a Cat. 1 Type J or Type F application.

8. The sponsor should provide the interim data from D811C00001 when available to provide further evidence in support of efficacy, safety, use in the elderly, and use with co-morbidities. This would be a Cat. 1 Type J or Type F application, depending upon the PI changes proposed.

9. The sponsor is to provide updates to the TGA in relation to additional information relevant to efficacy of COVID -19 vaccine Astra Zeneca against new and emerging variants of COVID-19.

10. The sponsor is to provide further information to the TGA in relation to use of the COVID-19 vaccine with influenza vaccines when available.

11. The sponsor is to provide the TGA with updates of the studies in the pharmacovigilance plan in relation to the safety of the vaccine in pregnancy, the elderly, the immunosuppressed and those with co-morbidities with the PSUR every 6 months.

Non-clinical

12. The sponsor should submit the following studies for review by the TGA when they are available. The submission type would be a cat 1 type H were no update to the Pi is required, or cat 1 type J where an update to the PI is required.
    a. Biodistribution study
    b. Developmental and reproductive toxicity final report

Medicine Labels

13. Unless otherwise agreed to by the Secretary following an application under section 9D of the Act, the product must only be supplied with the following labels:
    i) the international label, referred to here as the 'EU labels' for 10 doses per vial as follows:
        A) EU Anangi carton label (see copy at Attachment 5)
        B) EU Anangi vial label (see copy at Attachment 6)
        C) EU Catalent Stickers (see copy at Attachment 7)

    The sponsor will develop Australian-specific labels for the product, that conform with all relevant Australian labelling requirements, and will take all reasonable steps to implement such labelling before the end of the provisional registration period referred to in subsection 29(3) of the Act (being the period of 2 years starting on the day specified in the ARTG certificate of registration) (noting that, consistent with paragraph 28(5)(aaa) of the Act, changes to such matters as labels that have been agreed to as part of an evaluation under section 25 of the Act may only occur following submission under section 9D of a 'variation' application and approval by the TGA).

Quality

14. Drug Substance (AZD1222) and Drug Product manufacturing processes and testing: the sponsor should provide additional validation and comparability data and implement a QC suitable semi-quantitative/qualitative batch release test for transgene expression as detailed, and according to the due dates provided, in commitments made in eCTD Submission Version 0007 dated 5 February 2021, Module 1.03, Responses to Questions – Quality.

15. Stability: the sponsor should provide additional information on the stability of the Drug Substance (AZD1222) and Drug Product in monthly updates starting March 2021. These updates should report all available testing results for both the Drug Substance and the Drug Product, identify any out of specification results and discuss any emerging adverse trends.

16. Container Safety: To confirm the quality of the container closure system, the sponsor should provide leachables study data that should be available in March 2021. This includes up to 3 months of Stage 2 simulated leachables data for all 4 elastomeric stoppers (West 4432/50, West 4023/50, Datwyler FM259 and Daiko D21-7S) for intended commercial use.

17. Endotoxin safety aspects of the Drug Product: the sponsor should commit to providing the following data where applicable to DP destined for release in Australia (ie from the Catalent Anagni and IDT Biologika GmbH sites) when it becomes available.

18. Validation of Analytical Procedures: It is expected that the endotoxin inhibition/enhancement (test for interfering factors) data for the 3 DP lots as promised in the dossier will be provided from the above manufacturing sites when available.

19. **Batch Release Testing and Compliance**

It is a condition of registration that all independent batches of COVID-19 Vaccine AstraZeneca (ChAdOx1-S) vaccine imported into Australia are not supplied for distribution by or on behalf of the Sponsor until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.

For each independent batch of the product imported into Australia, the Sponsor must supply the following:

- A completed Request for Release Form, available from vaccines@health.gov.au.
- Complete summary protocols for manufacture and QC, including all steps in production in the agreed format.
- At least 10 (ten) vials (Samples) of each manufacturing batch of COVID-19 Vaccine AstraZeneca (ChAdOx1-S) with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted) representative of all batches of product seeking distribution in Australia.
- At least 5 (five) vials (Samples) of any further consignments of a manufacturing batch COVID-19 Vaccine AstraZeneca (ChAdOx1-S) with the Australian approved labels, PI and packaging (unless an exemption to supply these has been granted). Further consignments cover batches previously supplied to TGA for the purposes of batch release testing but are seeking to be supplied again.
- If the manufacturing batch has been released in Europe or United Kingdom a copy of the EU Official Control Authority Batch Release (OCABR) certificate (or equivalent from the UK) must be provided.
- Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Sponsors must provide all requested Samples and data in sufficient time (at least 5 business days) prior to any distribution date to allow the TGA to perform testing and review. Distribution of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

Samples and data should be forwarded to the Biotherapeutics Section, Laboratories Branch before release of each batch and with sufficient lead time to allow for Laboratories Branch testing. The address for courier delivery is:

ATTN: Batch Release Coordinator,
Batch Release Unit,
TGA Laboratories Branch,
136 Narrabundah Lane,
Symonston, ACT 2609.

The shipments (including reagents) to TGA are the responsibility of the Australian Sponsor/Agent who will be required to facilitate the import and customs clearance process.

20. **Certified Product Details**

An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) https://www.tga.gov.au/guidance-7-certified-product-details should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescription-medicines]. The CPD should be sent as a **single bookmarked PDF** document to Vaccines@health.gov.au as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

21. The actual date of commencement of supply is to be notified to the Branch Head, Prescription Medicines Authorisation Branch, TGA. Should it be decided not to proceed to supply, notification to this effect should be provided.

RMP

22. COVID-19 Vaccine AstraZeneca is to be included in the Black Triangle Scheme. The PI and CMI for COVID-19 Vaccine AstraZeneca must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

23. The COVID-19 Vaccine AstraZeneca EU-Risk Management Plan (RMP) (Version 1.0 Succession 5, dated 2 February 2021, data lock point 4 November 2020), with Australian Specific Annex (Version 1.0 Succession 4, dated 4 February 2021), included with submission PM-2020-06115-1-2 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

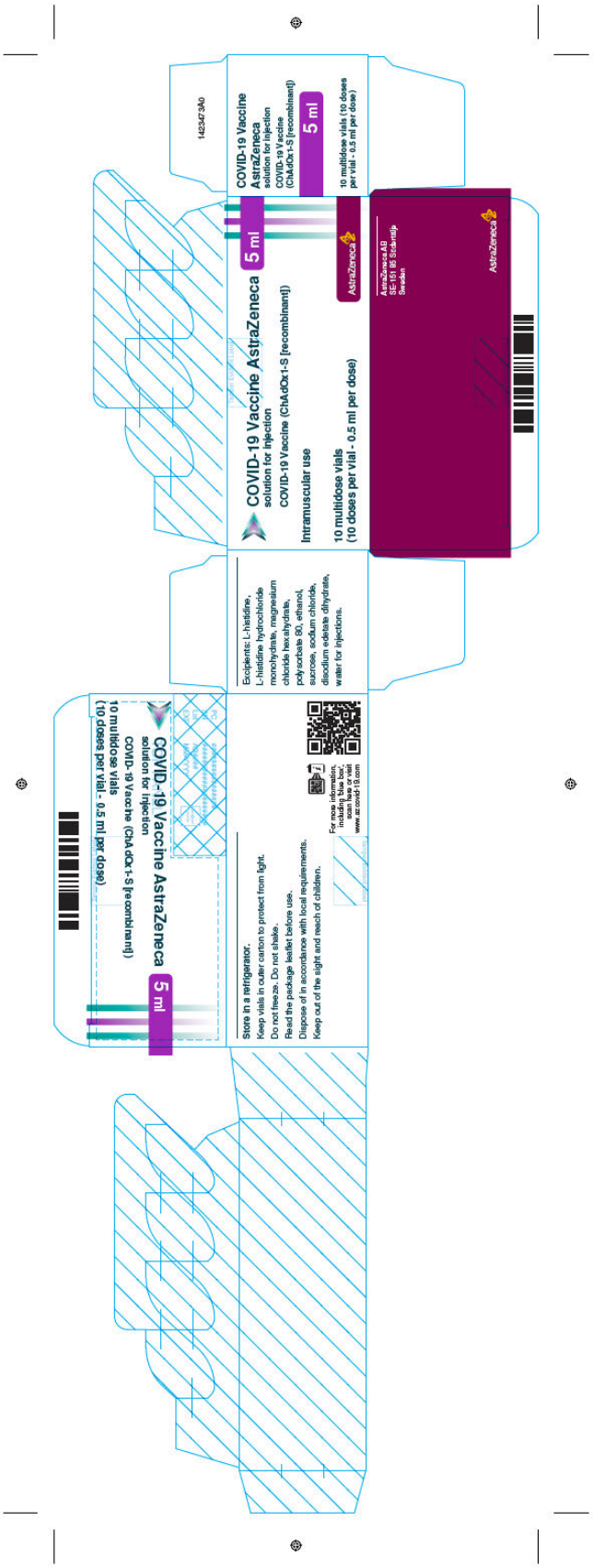
Unless agreed separately between the Sponsor and the TGA, the first report must be submitted to TGA no later than six calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than six monthly until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Additional to the routine submission of the routine PSURs, expedited monthly, safety summary reports (including safety data for patients in Australia) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

Attachment 5

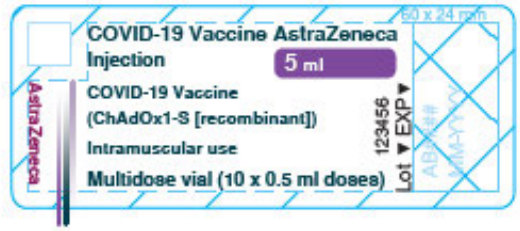
(Carton label shown without varnish)



[redacted]

Attachment 6

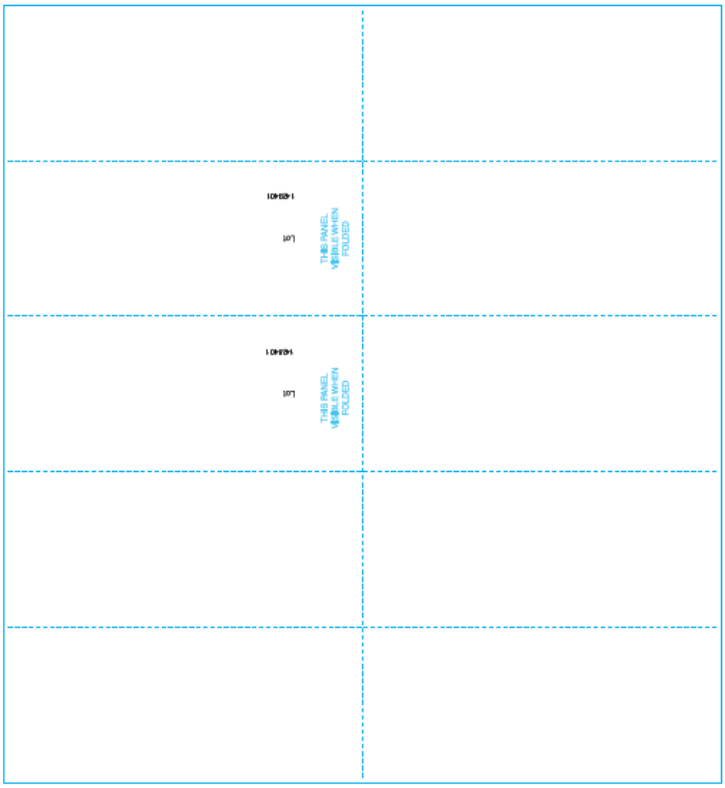
(Vial label shown without varnish)



[redacted]

Attachment 7

(Sticker format – Shown without varnish)



[redacted]

Attachment 5

(Enlarged sticker format – Shown without varnish)