PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CORONAVAC 600 SU (3 µg) suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml vial or 1 ml pre-filled syringe contains 0,5 ml.

A single dose of 0,5 ml contains 600 SU (3 µg) of inactivated SARS-CoV-2 virus produced in Vero cells, adsorbed on aluminium hydroxide (0,225 mg).

Sugar free and preservative free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.

CORONAVAC is an opalescent aqueous suspension (pH: 6,8 – 7,8).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CORONAVAC is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 to 59 years age.

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

4.2 Posology and method of administration

Posology

Individuals 18 to 59 years of age:

CORONAVAC is administered as a course of two doses of 0,5 ml each.

Dose 1: at the start date

Dose 2: 14 to 28 days after first dose.

If the second dose is inadvertently administered earlier than 2 weeks after the first, the dose does not need to be repeated.

If the second dose is inadvertently delayed beyond 4 weeks, it should be given at the earliest possible opportunity.

It is recommended that all vaccinated individuals receive two doses. According to the current recommendation, the same product should be used for both doses. (see section 5.1).

Paediatric population

The safety and efficacy of CORONAVAC in children and adolescents (less than 18 years of age) have not yet been established.

Method of administration

CORONAVAC is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, intravenously, subcutaneously or intradermally.

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

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

For instructions on handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to inactivated SARS-CoV-2 virus or to any of the excipients of CORONAVAC listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicines, the name and the batch number of the administered vaccine should be clearly recorded, as per the prescribed instructions.

Hypersensitivity and anaphylaxis

Appropriate medical treatment and supervision should always be readily available for immediate use in case of anaphylactic reaction following the administration of the vaccine. Individuals shall be observed for at least 15 minutes on site after injection. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of CORONAVAC.

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.

Neurological disorders

In patients with severe neurological conditions (such as transverse myelitis, Guillain-Barré syndrome, demyelinating diseases, etc.) CORONAVAC should be used with caution.

Thrombocytopenia and coagulation disorders

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 has been evaluated in a limited number of individuals living with HIV in China and Brazil. The efficacy of the vaccine may be lower in these 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 14 after the first dose of CORONAVAC.

Vaccination with CORONAVAC may not protect all vaccine recipients (see section 5.1).

Excipients with known effect

This medicine contains less than 1 mmol sodium (23 mg) per 0,5 ml dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed. Concomitant administration of CORONAVAC with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of CORONAVAC in pregnant women.

Animal reproductive toxicity studies have been completed. Based on results from the preliminary study, no effects are expected on development of the foetus (see section 5.3).

The safety of CORONAVAC during pregnancy has not been established.

Breastfeeding

It is unknown whether CORONAVAC is excreted in human milk.

The safety of CORONAVAC during lactation has not been established.

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

CORONAVAC has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 such as dizziness and drowsiness may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The safety of CORONAVAC has been evaluated based on analysis of pooled data from 4 on-going randomized, blinded, controlled clinical trials in China and Brazil. A total of 14 572 participants ≥ 18 years of age were enrolled in such studies, of which 7 654 subjects (age range, 18 ~ 84 years; male/female: 1:2.3) received at least one dose of COVID-19 vaccine and 6 399 received two doses. The median duration of follow-up was 28 days after the last dose.

The most frequently reported adverse reactions in these studies were injection-site pain (50,29 %), headache (28,02 %), fatigue (13,46 %), muscle pain (9,73 %), diarrhoea (6,77 %), nausea (6,53 %). 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 elderly (≥ 60 years).

As of the 23rd May 2021, 276,54 million doses of the COVID-19 vaccine have been supplied in China. According to the immunisation procedure of 2 doses with an interval of 14 to 28 days, the number of people vaccinated is estimated to be 138,27 million. The cumulative doses of the COVID-19 vaccine supplied in other countries/regions are 220,44 million doses. Based on a two-dose immunisation procedure with an interval of 14 to 28 days, the number of vaccinated people is estimated to be 110,22 million. Therefore, the total number of people who have used the vaccine is estimated to be 248,49 million.

As of the data lock point, the most frequently reported adverse reactions were fever (14,65 %), atopic dermatitis (11,02 %), dizziness (9,49 %), fatigue (6,63 %), nausea (5,71 %), headache (3,75 %), vomiting (3,47 %), myalgia (1,76 %).

A total of 295 new and serious adverse reactions (including 198 cases to be determined) were collected, including 36 cases of anaphylactic shock, 15 cases of allergic purpura, 14 cases of cerebral infarction, 13 cases of cerebral haemorrhage, 7 cases of Bell's palsy, 11 cases of laryngeal edema, and 8 cases of Guillain-Barré syndrome.

b. Summary of adverse events

Adverse drug reactions observed during clinical studies are organized by MedDRA System Organ Class (SOC). Frequency categories 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 < 1/1 000), not known (cannot be estimated from the available data. [(2)]

MedDRA System Organ Class (SOC)	**Frequency**	**Adverse reactions**
Immune system disorders	Uncommon	Hypersensitivity
	Rare	Anaphylactic shock Acute disseminated encephalomyelitis
Metabolism and nutrition disorders	Common	Decreased appetite
Nervous system disorders	Very common	Headache
	Uncommon	Tremor Dizziness Drowsiness
	Rare	Hyposmia Bell's palsy Facial paralysis Brain haemorrhage Brain infarction Cerebrovascular accident Guillian Barré syndrome Demyelination

MedDRA System Organ Class (SOC)	**Frequency**	**Adverse reactions**
Eye disorders	Rare	Ocular congestion Eyelid oedema
Ear and labyrinth disorders	Rare	Sudden hearing loss
Vascular disorders	Uncommon	Flushing
	Rare	Hot flashes Thrombosis Henoch-Schönlein purpura
Respiratory, thoracic and mediastinal disorders	Common	Cough Rhinorrhoea Oropharyngeal pain Nasal congestion
	Rare	Nosebleed/epistaxis Larynx oedema
Gastrointestinal disorders	Common	Nausea Diarrhoea Abdominal pain
	Uncommon	Vomiting
	Rare	Abdominal distension Constipation
Skin and subcutaneous	Common	Pruritus

MedDRA System Organ Class (SOC)	**Frequency**	**Adverse reactions**
tissue disorders	Uncommon	Mucocutaneous rash
	Rare	Allergic purpura
Musculoskeletal and connective tissue disorders	Common	Myalgia Arthralgia
	Rare	Muscle spasms
General disorders and administration site conditions	Very common	Vaccination site pain Fatigue
	Common	Vaccination site swelling Vaccination site pruritus Vaccination site erythema Vaccination site induration Chills
	Uncommon	Fever (Axillary temperature ≥ 37,3 °C) Vaccination site warmth Oedema

Characteristics of known adverse reactions

As of 23rd May, 17 445 episodes of adverse events following immunisation (AEFIs) have been reported, mainly involving general disorders and administration site conditions, gastrointestinal disorders, and nervous system disorders, manifested as fever, asthenia, nausea, vomiting, dizziness and headache. A total of 14 cases of known serious adverse reactions were identified, with an estimated rate of 0,05/million doses. A total of 9 323 cases of adverse reactions possibly related to the vaccine were collected. Among them,

the outcome of 8 cases was known, that of 20 cases was aggravating, and 714 cases were treated.

Characteristics of new adverse reactions

As of 23rd May, a total of 9 412 episodes of adverse events following immunisation (AEFIs) have been reported, mainly involving general disorders and administration site conditions, skin and subcutaneous tissue disorders, and nervous system disorders, manifested as chest discomfort, rash and urticaria. A total of 270 cases of new and serious adverse reactions were reported, with an estimated rate of 0,98 cases/million doses. A total of 8 686 cases of new adverse reactions possibly related to the vaccine were collected. Among them, the outcome of 5 cases was known, that of 13 cases was aggravating, 963 cases were treated, and 25 cases of death were reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Alternatively contact Curanto Pharma (Pty) Ltd at +27 12 004 0913 or send an email to regulatory@curantopharma.co.za

4.9 Overdose

In Phase I/II clinical trials, where a higher dose (1 200 SU/dose/0,5 ml) was administered, among 286 adults and 245 elderly people who received this vaccine, no significant difference in the overall adverse reactions had been observed.

In the event of an overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.30.1 Biologicals antigens

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

Mechanism of action

COVID-19 Vaccine (Vero Cell), Inactivated is an inactivated whole virion (CZ02 Strain) and aluminium adjuvanted vaccine.

On injection, the inactivated viruses are engulfed by antigen-presenting cell (APCs) and different epitopes are presented to the immune system to trigger the immune response of the human body.

Clinical efficacy

The efficacy and safety of COVID-19 (Vero Cell) aluminium adjuvanted vaccine were studied in two multicentre, randomized, double-blind, placebo-controlled clinical trials; one carried out among medical workers aged 18 and above in Brazil and the other in mixed population of medical staff or not, aged 18-59 in Turkey. The pre-defined primary efficacy endpoint was the incidence of symptomatic cases of virologically confirmed COVID-19 two weeks after the second vaccination in both clinical trials. Participants were included into the clinical trial in Turkey only with a negative serostatus at baseline, while participants were included into the clinical trial in Brazil irrespective of their baseline serostatus. The main analysis method of vaccine efficacy in Brazil is based on person-year incidence, and the that in Turkey is based on incidence rate. All COVID-19 cases were confirmed by the Endpoint Adjudication Committee.

1) Phase III clinical trial in Brazil

The target population of phase III clinical trial in Brazil was medical staff who works in direct contact with possible or confirmed COVID-19 cases. Participants have received two doses (0,5 ml each) of this product in a 14 days interval. A total of 12 396 subjects (incl. 1 1764 adults aged 18~59 years and 632 elderly aged 60 years and above) were enrolled into the trial, among which 9 823 were included into the Per-Protocol Set. Regarding the per-protocol population, male/female ratio was 1:1.8, age range was 19~84 years old, and proportion of subjects aged 60 years and above was 4,3 %. Totally 253 effective cases were detected from the per-protocol population during the monitoring period, i.e., more than 14 days after the second dose vaccination.

The overall efficacy against all COVID-19 cases was 50,65 % (95 %CI: 35,66~62,15), and that against hospitalized, severe COVID-19 cases was 100 % (56,37~100,00) (Table 3). The average follow-up time for the subjects receiving the product was 70,3 ± 25,6 days, and the median follow-up duration was 73,0 days.

The efficacy against all COVID-19 cases among the population with or without SARS-CoV-2 history was comparable, i.e.,49,53 % (-101,81~87,38) and 50,52 % (33,63~63,11) respectively (Table 4); efficacy against all COVID-19 cases among the adults and elderly was comparable, i.e., 50,66 % (35,75~62,11) and 51,11 % (-166,93~91,04) respectively (Table 5).

Table 3 Efficacy against COVID-19, 14 Days after 2 Doses of Vaccination in Phase III Clinical Trial in Brazil

Group	The Vaccine (N=4 953)			Placebo (N=4 870)			Vaccine Efficacy (%) (95 % CI)
	Number of cases	Person-year of exposure	Person-year incidence (%)	Number of cases	Person-year of exposure	Person-year incidence (%)	
COVID-19 cases*	85	754,6	11,03	168	736,5	22,34	50,65 (35,66; 62,15)
WHO-Grade 4 and above#	0	755,6	0,00	10	738,2	1,35	100,00 (56,37; 100,00)

*Anyone who has 1) two or more of the symptoms of category A or at least one symptom of category B; or 2)

has the imaging characteristics of COVID-19; and 3) detection of SARS-CoV-2 nucleic acid in a clinical sample. Category A symptoms (last for at least two days) include fever, chill, sore throat, fatigue, nasal congestion or nasal flow, body pain, muscle pain, headache, nausea or vomiting, diarrhea; Category B symptoms include cough (lasts for at least two days), newly developed taste or smell disorders (lasts for at least two days), shortness of breath or difficulty breathing.

WHO clinical progression scale was adopted, referring to the following document: WHO Working Group on the Clinical Characterisation and Management of COVID-19 Infection. A minimal common outcome measurement set for COVID-19 clinical research. Lancet Infect Dis. 2020 Aug; 20(8): e192-e197.

Table 4 Protective Efficacy against COVID-19 More than 14 Days after Two Doses of Vaccination in the Population with or without SARS-CoV-2 Exposure History

Sub-group	Vaccine				Placebo				Vaccine Efficacy (%) (95% CI)
	Number of participants	Number of patients	Person-year of exposure	Person-year incidence (%)	Number of participants	Number of patients	Person-year of exposure	Person-year incidence (%)	
Without SARS-CoV-2 exposure history*	3 637	67	560,8	13,3	3 587	133	550,7	26,8	50,52 (33,63; 63,11)
With SARS-CoV-2 exposure history#	401	3	50,5	5,9	408	6	51,3	11,7	49,53 (-101,81; 87,38)

*This is defined as a negative result in both the testing of SARS-CoV-2 nucleic and that of serum antibody against SARS-CoV-2.

#This is defined as a positive result in either the testing of SARS-CoV-2 nucleic or that of serum antibody against SARS-CoV-2.

Table 5 Protective Efficacy against COVID-19 More than 14 Days after Two Doses of Vaccination in Adults and Elderly

Sub-group	Vaccine				Placebo				Vaccine Efficacy (%) (95% CI)
	Number of participants	Number of patients	Person-year of exposure	Person-year incidence (%)	Number of participants	Number of patients	Person-year of exposure	Person-year incidence (%)	
18~59 years	4 741	83	736,0	11,3	4 663	164	718,2	22,8	50,66 (35,75; 62,11)
≥ 60 years	212	2	18,6	10,8	207	4	18,3	21,9	51,11 (-166,93; 91,04)

2) Phase III clinical trial in Turkey

The target population in Turkey contains high-risk healthcare professionals (K-1) and regular population (K-2). As of December 23, 2020, a total of 7 371 subjects were enrolled, including 918 subjects in K-1 and 6 453 subjects in K-2. Among which, 1 322 subjects completed two doses vaccination and entered the monitoring period of 14 days after the second dose. Based on the analysis for 29 cases, protective efficacy after inoculation 2 doses of this vaccine according to 0,14 days program is 91,25 % (95 % CI: 71,25 – 97,34) (Table 6).

Table 6 Protective Efficacy against COVID-19, More than 14 Days after Two Doses of Vaccination in Phase III Clinical Trial in Turkey

Group Index	The Vaccine (N=752)		Placebo (N=570)		VE (%) (95 % CI)
	Number of cases	Incidence rate (%)	Number of cases	Incidence rate (%)	
COVID-19	3	0,40	26	4,56	91,25 (71,25; 97,34)

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology (single dose toxicity, repeated dose toxicity and active systemic anaphylaxis) and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium hydroxide (adjuvant)

Disodium hydrogen phosphate

Monosodium dihydrogen phosphate

Sodium chloride

Water for injection

6.2 Incompatibilities

CORONAVAC must not be diluted or mixed with the other medicines.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a refrigerator (2 - 8 ºC).

Store in the original package in order to protect from light.

Do not freeze.

After first opening, the vaccine should be used immediately.

6.5 Nature and contents of container

Pre-filled syringe: Single dose 1 ml pre-filled syringe (type I glass barrel) with a rubber plunger stopper, stainless steel needle and plastic tip cap.

Vial: Single dose 2 ml vial (type I glass) with a rubber stopper and aluminium-plastic combination cap.

Pack size: 10 pre-filled syringes or 40 vials per cardboard box.

6.6 Special precautions for disposal and other handling

Handling instructions

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

The vaccine should be inspected visually for foreign particulate matter and discoloration prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine.

The vial and the pre-filled syringe should be inspected visually for cracks or any abnormalities, such as evidence of tampering prior to administration. In the event of visual cracks or abnormalities, do not administer the vaccine.

Shake well before use.

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

Disposal

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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14 June 2022

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