Summary of Product Characteristics (SmPC)

COVILO is indicated for active immunization of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19).
This medicinal product is under the conditional approval of modern medicine for human use in emergency situation during a pandemic crisis.
The prescribed physician is required to report any adverse reactions to the Food and Drug Administration.
Please read the information carefully.

COVILO

1. Name of the Medicinal Product

1.1 Product Name

Generic name: COVID-19 Vaccine (Vero Cell), Inactivated
Trade name: COVILO

2. Qualitative and Quantitative Composition

Each dose (0.5 mL) of vaccine contains SARS-CoV-2, 19nCoV-CDC-Tan-HB02 strain (inactivated) 6.5 U

COVILO is formulated with SARS-CoV-2 strain which is inoculated on the Vero cells for culturing, virus harvesting, β-propiolactone inactivation, concentration and purification, then adsorbed with aluminum hydroxide to form the liquid vaccine.

For full list of excipients, see section 6.1

3. Pharmaceutical Form

Suspension for injection
The product is a semi-transparent suspension with display a slightly white to off-white color after shaking, could be layered by precipitation, and the precipitation can be easily dispersed by shaking.

4. Clinical Particulars

4.1 Therapeutic Indication

COVILO is indicated for active immunization of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19).

For elderly population, see section Elderly population.

4.2 Posology and Method of Administration

Posology

COVILO vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 21- 28 days after the first dose (see section 5.1 Pharmacodynamic properties).

It is recommended that individuals who receive a first dose of COVILO complete the vaccination course with COVILO (see section 4.4 Special warnings and special precautions for use).

Elderly population

A relatively small number of participants in the phase 3 clinical trial were aged 60 years or over, and there were no cases of COVID-19 in either the vaccine or the placebo group in this age category; *thus, vaccine efficacy could not be estimated.* Seropositivity rate induced by the COVILO in older persons were similar to those in younger adults and neutralizing antibody titres were substantial, although lower in the older adult age group.

Preliminary and not yet peer-reviewed post-introduction observational data from Bahrain suggest a vaccine effectiveness across all age-groups of more than 80%, including persons aged ≥ 60 years. Supportive immunogenicity data together with these preliminary observational data suggest that COVILO is likely to have a protective effect in older persons, although whether at an equivalent level as in younger adults needs to be shown in further studies.

As the risk of severe disease and death due to COVID-19 increases steeply with age, older adults are then identified as a priority group. Based on the currently very limited efficacy and safety data in individuals ≥ 60 years old, it is recommended that administration of COVILO only be carefully considered when the potential benefits outweigh any potential risks for elderly individuals.

No dosage adjustment is required.

Pediatric population
The safety and efficacy of COVILO in children and adolescents (aged <18years old) have not yet been established. No data are available.

Method of Administration
COVILO is for intramuscular (IM) injection only, preferably in the deltoid muscle.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

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

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

For instructions on administration, see section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications
Do not use COVILO in individuals who have hypersensitivity to the active substance or to any of the excipients. (Please see section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and 6.1 List of excipients).

4.4 Special Warnings and Precautions for Use
Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
As per good medical practices, the individuals should be interviewed and reviewed all past history (especially the previous immunization and the potential of adverse reactions) before vaccination.

As with all other injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation for at least 30 minutes is recommended following vaccination.

Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties and non-epileptic seizures with no apparent physiological basis. It is important that procedures are in place to avoid injury from faints.

Concurrent illness
As with other vaccines, administration of COVILO 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 (IM), COVILO 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.

Immunocompromised individuals
It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.

Duration of protection
The duration of protection has not yet been established.

Limitations of vaccine effectiveness
Individuals may not be fully protected until 14 days after their second dose. As with all vaccines, vaccination with COVILO may not protect all vaccine recipients.

Interchangeability
No data are available on the use of COVILO in persons that have previously received a full or partial vaccine series with another Covid-19 vaccine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, and is considered to be essentially sodium-free.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction.
No interaction studies have been performed.

Concomitant administration of COVILO with other vaccines has not been studied.

4.6 Fertility, Pregnancy, and Lactation
Pregnancy
No data are available for the use of COVILO in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development.

Administration of COVILO in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breast Feeding
No data are available for the use of COVILO in breastfeeding women. It is unknown whether COVILO is excreted in human milk.

Administration of COVILO in breast feeding should only be considered when the potential benefits outweigh any potential risks for the mother and infant.

Fertility
Preliminary 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 Machine
COVILO has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive and use machines.

4.8 Undesirable Effects
Summary of the safety profile
The safety of this vaccine is evaluated through the domestic and international clinical trials and are still ongoing. The domestic phase 1/2 clinical trials are randomized, double-blinded and placebo parallel controlled to preliminarily evaluate the safety and immunogenicity of this product for adults over 18 years old. The international phase 3 clinical trial is an international multi-center, randomized, double-blinded, placebo parallel controlled to evaluate the protective efficacy, safety and immunogenicity of this product. Active follow up of the safety data of 0~21/28 days after each vaccination to observe the occurrence of adverse events was conducted. Attention was paid to the serious adverse events occurred within 12 months after full-course vaccination at the same time.

In the COVIV01 study, there were no significant differences in the incidence of total adverse events (AEs) and systemic adverse reactions among the study arms. Systemic AEs were mainly fever, and local AEs were mainly pain. No ≥grade 3 AE was reported in the vaccine arms. Serious adverse events (SAEs) were reported in 12 participants; all were assessed as unrelated to the vaccine.

In the second interim analysis of the COVIV02 study, as of 31 December 2020, 43,851 and 42,501 participants had completed, respectively, the first and second vaccine or placebo doses. Among the 14,634 participants who received the vaccine, 6,570 experienced a total of 16,057 AEs, for an incidence of 44.90%, which was comparable to the placebo arm (49.01%). Solicited AEs were reported in 20.45% and 22.25% of the vaccine and the placebo groups, respectively. There were 73 ≥grade 3 AEs in the vaccine group (0.39%), and 73 (0.43%) in the placebo arm. The incidences of SAEs in the vaccine and placebo groups were also comparable (0.40% vs. 0.55%). Two SAEs were considered to be possibly causally related to the vaccine (serious nausea and inflammatory demyelination syndrome/acute encephalomyelitis. In adults 60 years of age and older, the safety profile was comparable to that of younger adults, but they presented lower reactogenicity. In this age group, no SAE was observed. In the bridging study (COVIV05), no significant differences were observed between the AEs reported from participants receiving vaccines produced at commercial scale and pilot scale.

The incidence for ADRs (CIOMS recommendation) can be presented as
- very common (≥10%),
- common (1-10%, including 1%),
- occasional (0.1-1%, including 0.1%),
- rare (0.01-0.1%, including 0.01%),
- very rare (<0.01%)

The summary overview of the safety data of the vaccine in phase 1/2 and phase 3 clinical trials are as follows.

(1) ADRs at the injection site
Very common: Pain;
Occasional: Redness, swelling, induration, pruritus;
Rare: Erythema

(2) Systemic ADRs
Very common: Headache;
Common: fever, fatigue, myalgia, arthralgia, cough, dyspnea, nausea, diarrhea, pruritus;

Occasional: dizziness, anorexia, vomiting, oropharyngeal pain, dysphagia, running nose, constipation, hypersensitivity;

Rare: acute allergic reaction, lethargy, drowsiness, difficulty falling asleep, sneezing, nasopharyngitis, nasal congestion, dry throat, influenza, hypoesthesia, limb pain, palpitations, abdominal pain, rash, abnormal skin mucosa, acne, ear discomfort, lymphadenopathy;

Very rare: chills, taste dysfunction, loss of taste, paresthesia, tremor, attention disorder, epistaxis, asthma, throat irritation, tonsillitis, physical discomfort, neck pain, jaw pain, neck lump, mouth ulcers, toothache, esophagus disorders, gastritis, fecal discoloration, ophthalmodynia, blurred vision, eye irritation, earache, tension, hypertension, hypotension, urinary incontinence, delayed menstruation.

(3) Severity of ADRs

The severity of ADRs for the vaccine observed in clinical trials is mainly grade 1 (mild), and the incidence of grade 3 and above solicited ADRs is 0.44%. No grade 4 ADRs related to this product are reported. The grade 3 ADRs at the injection site reported in the clinical trials include: pain, erythra, pruritus; the grade 3 systemic ADRs include: fever, fatigue, headache, myalgia, arthralgia, cough, dyspnea, nausea, vomiting, diarrhea, dysphagia.

(4) Serious Adverse Event (SAE)

Up to 31 October 2020, among all observed SAEs during the international Phase Ⅲ clinical trials, one subject with serious nausea, vomiting and other symptoms was confirmed to be related to the vaccine. This subject was hospitalized and cured. Another subject with 'right upper limb weakness and cannot speak clearly' was diagnosed as 'inflammatory demyelination syndrome, multiple sclerosis (MS), clinical isolated syndrome (CIS), and acute disseminated encephalomyelitis (ADEM)' by hospital. Whether this case is related to the vaccine cannot be determined.

4.9 Overdose

There is no experience of overdose.

There is no specific treatment for an overdose with COVILO. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

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

Mechanism of Action

The vaccine induces the production of neutralizing antibodies against SARS-CoV-2 virus.

Clinical Overview

The evidence to support the COVILO comes from interim results of a phase 1/2 study (COVIV01), conducted in individuals from 3 years of age, which included 2,128 participants in China and 112 in Pakistan; a phase 3 study (COVIV02), conducted in the United Arab Emirates (UAE), Bahrain, Egypt, and Jordan, involving 45,000 participants 18 years of age and above; and a double-blind randomized study (COVIV05) conducted in China aimed at immunological bridging of commercial scale and pilot scale vaccines and the assessment of lot-to-lot consistency.

COVIV01 and COVIV02 were designed as double-blind, randomized, placebo-controlled-trials and are still ongoing. In COVIV01, three formulations (low dosage – 2 μg/0.5 mL/dose –, middle dosage – 4 μg/0.5 mL/dose –, and high dosage – 8 μg/0.5 mL/dose –), and different combinations of number of doses and intervals between doses (1-dose schedule, 2-dose schedule – 14, 21, or 28 days apart –, and 3-dose schedule 28 days apart) were studied. A total of 96 subjects ≥ 60 years participated in this study. In COVIV02, 15,000 participants received two doses of COVILO 4 μg/0.5 mL on days 0 and 21, and 15,000 received placebo. The remaining 15,000 received

another experimental COVID-19 vaccine, manufactured by the Wuhan Institute of Biological Products, and no discussion was reported here.

Two other phase 3 studies are also ongoing but no results are said to be available. These are double-blind, randomized, placebo-controlled-trials conducted in Peru (COVIV03) and Argentina (COVIV04) in, respectively, 6,000 and 3,000 participants from 18 years of age.

Clinical Efficacy

Clinical efficacy of COVILO was based on the interim results of the phase III clinical study (CIVIV02) that was conducted to evaluate the immunogenicity, safety, and protective efficacy of two doses (21- day interval) of COVILO in healthy people aged 18 years and above.

Only data from interim analyses of the COVIV02 trial were submitted. The first interim analysis was conducted after >50 cases occurring after the second vaccine dose were identified, based on the data as of 31 October 2020 and the protective efficacy data as of 30 October 2020. The median follow-up of the participants at the time of this first interim analysis was only 35 days, which was considered insufficient.

A second interim analysis of the COVIV02 study, when data was available for 13,765 participants in the vaccine group (11,642 males, 13,556 aged 18-59 years) and 13,765 participants in the placebo arm (11,642 males, 13,559 aged 18-59 years) with a median follow-up at the time of data lock of 112 days was carried out when there were 116 cases, 21 out of them in the vaccine (COVILO) arm. For the primary analysis (laboratory-confirmed symptomatic COVID-19 cases 14 days after the second dose of the vaccine), the estimated protective efficacy was 78.89 % (95%CI 65.79%, 86.97%). Vaccine efficacy, calculated taking into consideration the person-years of follow-up, was 78.07% (95%CI 64.82%, 86.33%). For the hospitalization outcome, the vaccine efficacy estimate was 78.7% (95% CI 26.0%, 93.9%). Vaccine efficacy estimates were similar in males and females (point estimates of 78.4% and 75.6%, respectively). Vaccine efficacy in the elderly could not be estimated given that there were no cases in the vaccine and placebo arms. Available data were also not sufficient to estimate vaccine efficacy for participants with comorbidities and for severe COVID-19 cases (only 2 severe cases were observed in the placebo arm and none in the vaccine arm).

Immunogenicity

In the COVIV01 study, the mid-dose (4µg/0.5mL) provided 100% seroconversion of neutralizing antibodies in participants 18-59 years of age at 28 days after the second dose and 100% in the participants ≥60 years of age at 28 days after the third dose.

Cellular Immunity: The vaccine did not cause "obvious" inflammatory factor storms or abnormal proliferation of cellular responses. Antigen-specific cellular immunity was not reported. According to the manufacturer, Beijing Institute of Biological Products (BIBP), current results show that antibody levels did not decrease 3 months after vaccination (GMT being 233.6 [95% CI 176.2, 309.7] 28 days after the second dose, and 273.9 [95% CI 202.8, 370.0] 90 days after vaccination).

In the second interim analysis of the COVIV02 study, seroconversion of neutralizing antibodies in the vaccine group was 100% (95% CI 99.56, 100) compared to 16.07% (95% CI 13.64, 18.74) in the placebo group. Neutralizing antibody GMT were 152.6 (95% CI 146.0, 159.4) in the vaccine arm and 2.1 (95% CI 2.1, 2.2) in the placebo arm. Total binding antibody GMTs were 1,366.1 (95% CI 1,249.7, 1,493.3) and 8.9 (95% CI 8.1,9.8), respectively, in the vaccine and in the placebo arms. When stratified by age, seroconversion rates (neutralizing antibodies) were 99.52% and 100%, respectively, in the 18-59 and ≥60 years of age groups. GMT titers, however, were lower in the 60+ years of age arm.

Cross-neutralization studies with 20 SARS-CoV-2 isolates from China and other countries indicate that the sera from the participants could neutralise all these viral isolates. There are no results from cross-neutralisation tests using any of the recently emerging genetic variants. An independent study not included in the application claims a 1.6 reduction of neutralization of the South African variant (B.1.351 lineage).

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 repeat dose toxicity and reproductive and developmental toxicity.

6. Pharmaceutical Particulars
6.1 List of Excipients
Disodium hydrogen phosphate, sodium chloride, sodium dihydrogen phosphate, aluminum hydroxide.

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

6.3 Shelf Life
6 months from the date of manufacturing.

Use vaccine immediately after opening.

Please see expiry date on the outer carton.

6.4 Special Precautions for Storage
Store and transport between (2°C - 8°C) condition and protect from light. Do not freeze.

6.5 Nature and content of container
This is a liquid vaccine, and the inner packaging is a pre-filled syringe assembly or vial.

Pre-filled syringes (1-mL) is used for filling of each dose of vaccine. Each pre-filled syringe is composed of the needle cover, needle-bearing glass tube, plunger rubber cap and plunger stick.

Middle-borosilicate glass vial (2-mL) is used for filling of each dose of vaccine. Each vial is composed of film-coated middle-borosilicate glass vials, aluminum foil cap and film-coated rubber stopper.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
7.1 Marketing authorization holder in China
Name: Beijing Institute of Biological Products Co., Ltd.
Add: No. 6&9 Bo'xing 2nd Road, Economic-Technological Development Area, Beijing, P.R. China
Tel: +86 10 8722 0568
Fax: +86 10 8722 0568
Post Code: 100176
Website: http://www.bjbpi.com

7.2 Marketing authorization holder in Thailand

Biogenetech

Biogenetech Co., Ltd.
18 Soi Udomsuk 37, Sukhumvit 103 Rd., Bangjak, Prakanong, Bangkok 10260 THAILAND
Tel. 0-2748-9333 Fax. 0-2748-9393

8. Marketing Authorization Number(s)
8.1 Marketing Authorization Number in China: GYZZ S20200029, GYZZ S20200030
8.2 Marketing Authorization Number in Thailand: 1C 7/64 (NBC)

9. Date of First Authorization
9.1 Date of authorization in China: 30th December 2020
9.2 Date of authorization in Thailand: 28th May 2021

10. Date of Revision of the Text
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LABELLING INFORMATION

COVID-19 Vaccine (Vero Cell), Inactivated (COVILO)

0.5 mL Vial/Pre-filled Syringe

Suspension for Injection

Each dose (0.5 mL) contains:-
SARS-CoV-2, 19nCoV-CDC-Tan-HB02 strain (inactivated) 6.5 U

Intramuscular use

Single dose vial/pre-filled syringe
(1 dose per vial/pre-filled syringe - 0.5 mL per dose)

ยาควบคุมพิเศษ

Reg. No. 1C 7/64 (NBC)

CHINESE PACK	THAI PACK
Lot No.: ######	**Lot No.** ######
MFD.: YYYY/MM/DD	**MFD.:** YYYY/MM/DD
EXP.: YYYY/MM/DD	**EXP.** YYYY/MM/DD
SN ##### ##### ##### #####	**SN** ##############

Manufactured by:
Beijing Institute of Biological Products Co., Ltd.
No. 6&9 Bo'xing 2nd Road, Economic-Technological Development Area, Beijing, P.R. China

Batch released by:
Beijing Institute of Biological Products Co., Ltd.
No. 6&9 Bo'xing 2nd Road, Economic-Technological Development Area, Beijing, P.R. China

Imported by:
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