

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

COVIFENZ[®]

COVID-19 Vaccine (plant-based virus-like particles [VLP], recombinant, adjuvanted)

Emulsion for Intramuscular Injection

Multiple Dose Vial

(Each vial contains 10 doses of 0.5 mL after mixing with AS03 adjuvant)

Active Immunizing Agent

ATC Code: J07BX03



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TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION	3
1 INDICATIONS	3
1.1 Pediatrics.....	3
1.2 Geriatrics.....	3
2 CONTRAINDICATIONS	3
3 SERIOUS WARNINGS AND PRECAUTIONS	3
4 DOSAGE AND ADMINISTRATION	3
4.1 Dosing Considerations.....	3
4.2 Recommended Dose and Dosage Adjustment.....	3
4.3 Reconstitution.....	4
4.4 Administration.....	6
5 OVERDOSAGE	6
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	6
7 WARNINGS AND PRECAUTIONS	8
7.1 Special Populations.....	9
7.1.1 Pregnant Women.....	9
7.1.2 Breast-feeding.....	9
7.1.3 Pediatrics.....	9
7.1.4 Geriatrics.....	9
8 ADVERSE REACTIONS	9
8.1 Adverse Reaction Overview.....	9
8.2 Clinical Trial Adverse Reactions.....	10
9 DRUG INTERACTIONS	14
10 CLINICAL PHARMACOLOGY	14
10.1 Mechanism of Action.....	14
11 STORAGE, STABILITY AND DISPOSAL	14
12 SPECIAL HANDLING INSTRUCTIONS	14
PART II: SCIENTIFIC INFORMATION	15
13 PHARMACEUTICAL INFORMATION	15
14 CLINICAL TRIALS	15
14.1 Trial Design and Study Demographics.....	15
14.2 Study Results.....	16
15. MICROBIOLOGY	17
16. NON-CLINICAL TOXICOLOGY	17
PATIENT MEDICATION INFORMATION	19

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

COVIFENZ, COVID-19 Vaccine (plant-based virus-like particles [VLP], recombinant, adjuvanted), is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 to 64 years of age.

1.1 Pediatrics

The safety and efficacy of COVIFENZ in individuals younger than 18 years of age have not been established.

1.2 Geriatrics

The safety and efficacy of COVIFENZ in individuals 65 years and older have not been established.

2 CONTRAINDICATIONS

COVID-19 Vaccine (plant-based virus-like particles [VLP], recombinant, adjuvanted) is contraindicated in individuals who are hypersensitive to the active substance or to any ingredient in the formulation. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

3 SERIOUS WARNINGS AND PRECAUTIONS

At the time of authorization, there are no known serious warnings or precautions associated with this product.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

COVIFENZ is an emulsion for intramuscular injection. The antigen component of COVIFENZ is a suspension, which must be mixed 1:1 with the AS03 adjuvant emulsion component prior to administration. It should be administered by a trained healthcare professional authorized to deliver intramuscular injections.

4.2 Recommended Dose and Dosage Adjustment

Vaccination Schedule for Individuals 18 to 64 years of age

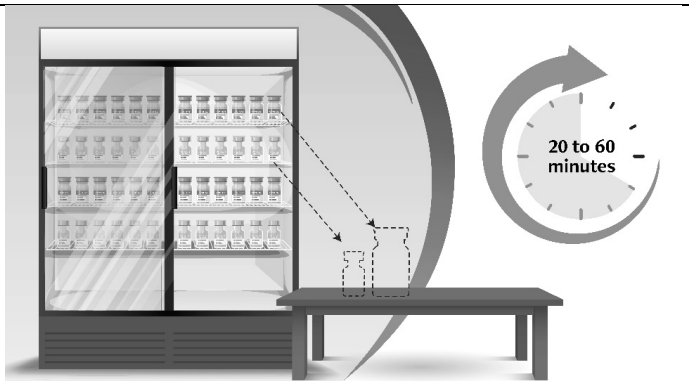
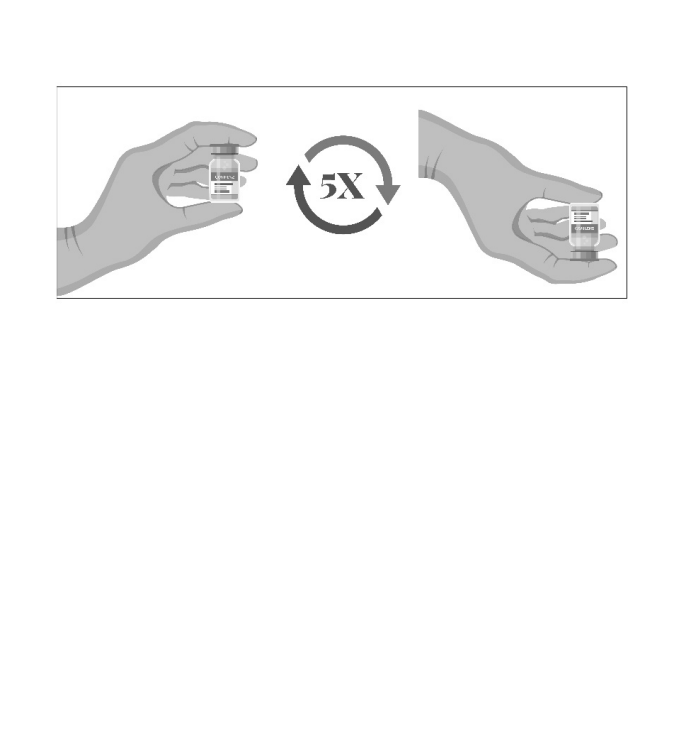
COVIFENZ is administered intramuscularly into the deltoid muscle, after mixing, as a series of two doses (0.5 mL each), 21 days apart.

There are no data available on the interchangeability of COVIFENZ with other COVID-19 vaccines to complete primary vaccination. Individuals who have received one dose of COVIFENZ should receive the second dose of COVIFENZ to complete the primary vaccination series.

4.3 Reconstitution

Check the expiry date on the antigen and adjuvant vials. Mixing of the COVIFENZ antigen with the adjuvant is required prior to administration.

Preparation for Administration:

Prior to mixing	
<p>1. Remove the antigen and adjuvant vials from the refrigerator and allow them to reach room temperature (no less than 20 minutes, no more than 60 minutes).</p>	
<p>2. Gently invert each vial 5 times or until homogeneity is obtained. <u>Do not vortex or mix vigorously (no shaking).</u></p> <p>3. Inspect the antigen and AS03 adjuvant vials for foreign matter, change in colour and / or leakage prior to mixing. If one of these conditions exist, the antigen or AS03 adjuvant vial must be discarded.</p> <ul style="list-style-type: none">• Antigen content should be transparent to opalescent, colorless to yellowish liquid suspension. It may contain visible white particulates.• AS03 adjuvant content should be whitish to yellowish homogenous milky liquid emulsion.	

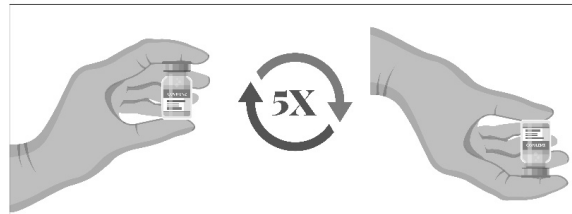
Mixing

4. Strict adherence to aseptic techniques must be followed.
5. Hold and keep the adjuvant vial upside down. Use a 5 mL syringe (at least 21- gauge needle) to fully withdraw the entire content of the adjuvant vial and transfer it to the larger antigen vial.
6. Do not mix COVIFENZ with other vaccines / products in the same syringe.



7. Gently invert the vial containing the mixed content a minimum of 5 times or until homogeneity is obtained. Do not shake vials or mix vigorously.

The concentration of the mixed vaccine, an emulsion for injection is 7.5 mcg / mL.



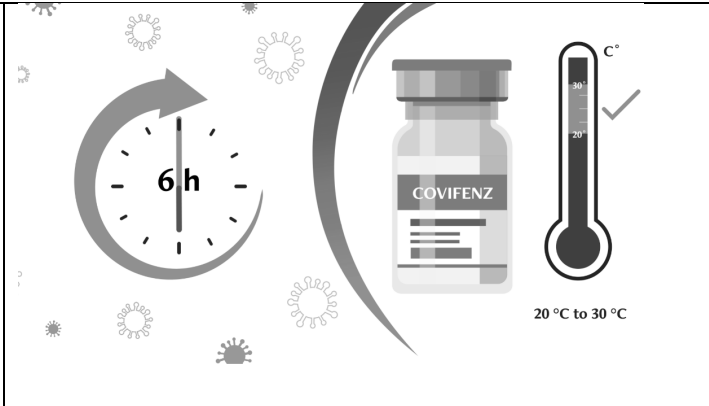
8. Prior to use, inspect for foreign matter, change in colour and/or leakage. If one of these conditions exists, the vaccine must not be used.

- The **mixed vaccine** should be a whitish to yellowish homogeneous milky liquid emulsion; otherwise, it must be discarded.

9. Record the time that the components were mixed on the antigen vial label.



10. The vaccine must be used within 6 hours and stored at room temperature (20 °C to 30 °C) until administered. Do not refrigerate. Protect from light. (See **11 STORAGE, STABILITY AND DISPOSAL**)



4.4 Administration

1. Before every administration, gently invert the vial until homogeneity is obtained.
2. Inspect for foreign matter, change in colour and/or leakage. If any of these conditions exists, the vaccine must not be administered.
3. Cleanse the vial stopper with a single-use antiseptic swab, allow to dry.
4. It is recommended to use a 1 mL syringe with a 23-gauge needle for vaccine withdrawal and injection.
5. Choose needle length based on the patient weight. Ensure that the needle is tightly attached to the syringe.
6. Withdraw a dose (0.5 mL) and administer into the deltoid muscle.

5 OVERDOSAGE

In the event of suspected overdose, monitoring of vital functions and symptomatic treatment are recommended. Contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

COVIFENZ is a sterile emulsion for intramuscular injection. It is supplied as two refrigerated containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant system (emulsion).

Each antigen vial must be mixed (mix ratio 1:1) with the entire content of the AS03 adjuvant vial prior to use. Once mixed with the adjuvant, the vial contains 10 doses of 0.5 mL of the formulation to be administered.

Each 0.5 mL dose contains 0.25 mL of the antigen component containing 3.75 mcg of the virus-like particles (VLP) SARS-CoV-2 spike (S) protein, 0.25 mL of the AS03 adjuvant and the non-medicinal ingredients listed in [Table 1](#) below.

Table 1. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Ingredients (per 0.5 mL vaccine dose)
Intramuscular injection	Emulsion, after mixing	<ul style="list-style-type: none"> • Antigen: 3.75 mcg of virus-like particles (VLP) of SARS-CoV-2 spike protein (original strain) • AS03 Adjuvant: 11.86 mg DL-alpha-tocopherol, 10.69 mg squalene, 4.86 mg polysorbate 80 and phosphate buffered saline. • Excipients: Polysorbate 80 Potassium phosphate monobasic anhydrous Sodium chloride Sodium phosphate dibasic anhydrous Water for injection May contain trace amounts of polyethylene glycol, kanamycin and carbenicillin

The antigen component is a sterile transparent to opalescent colorless to yellowish liquid suspension for injection that may contain visible white particulates, preservative-free.

AS03 adjuvant system is a sterile, homogenized, whitish to yellowish homogenous milky emulsion.

Immediately prior to use, the entire content of the AS03 vial is withdrawn and added to the antigen vial (mix ratio 1:1). The mixed final vaccine is a whitish to yellowish homogeneous milky liquid emulsion.

COVIFENZ is supplied in an outer pack containing a carton with antigen vials and a carton with adjuvant vials. Each carton contains 10 multidose vials of antigen and 10 multidose vials of adjuvant that must be mixed 1:1 prior to administration.

Each outer pack contains sufficient antigen and adjuvant to obtain 100 doses of 0.5 mL:

- 10 vials containing 2.5 mL of antigen suspension (10 doses of 0.25 mL)
- 10 vials containing 2.5 mL of AS03 adjuvant emulsion (10 doses of 0.25 mL)

The antigen vials are made of Type 1 clear borosilicate glass. The chlorobutyl vial stoppers are not made with natural rubber latex; and are capped with a green flip-off aluminum cap seal.

The adjuvant vials are made of Type 1 glass. The butyl vial rubber stoppers are not made with natural rubber latex and are capped with a light gold flip-off aluminum cap seal.

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose, anatomical site and route of administration, brand name and common name of the vaccine, the product lot number and expiry date.

7 WARNINGS AND PRECAUTIONS

General

The administration of COVIFENZ should be postponed in individuals suffering from any severe febrile illness or severe acute infection.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Individuals should be advised to bring up symptoms (e.g., dizziness, increases in heart rate, feeling short of breath, tingling sensations, or sweating) to the attention of the vaccination provider for evaluation. Procedures should be in place to avoid injury from fainting.

As with any vaccine, vaccination with COVIFENZ may not protect all recipients. Individuals may not be optimally protected until at least 7 days after their second dose of vaccine (see **14 CLINICAL TRIALS** section).

Acute Allergic Reactions

Although no events of anaphylaxis have been reported during the clinical trials, COVIFENZ should be administered with caution in individuals who have history of confirmed anaphylaxis to plant materials.

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 a vaccine.

Vaccine recipients should be kept under observation for at least 15 minutes after immunization; 30 minutes is a preferred interval when there is a specific concern about possible vaccine reaction.

A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVIFENZ.

Driving and Operating Machinery

COVIFENZ has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under **8 ADVERSE REACTIONS** may temporarily affect the ability to drive or use machines.

Fertility

It is unknown whether COVIFENZ has an impact on fertility. An animal study does not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see **16 NON-CLINICAL TOXICOLOGY**).

Hematologic

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.

Immune

Immunocompromised persons, including individuals receiving immunomodulatory therapy, may have a diminished immune response to the vaccine.

7.1 Special Populations

7.1.1 Pregnant Women

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

An animal study does not indicate any direct or indirect harmful effects with respect to reproductive or developmental toxicity (see [16 NON-CLINICAL TOXICOLOGY](#)).

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

7.1.2 Breast-feeding

It is unknown whether COVIFENZ is excreted in human milk. A risk to the newborns / infants cannot be excluded.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for immunization against COVID-19.

7.1.3 Pediatrics

The safety and efficacy of COVIFENZ in individuals younger than 18 years of age have not yet been established.

7.1.4 Geriatrics

The safety and efficacy of COVIFENZ in individuals 65 years and older have not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile in participants 18 to 64 years of age presented below is based on data generated from an ongoing Phase 3 portion of Study 021 (CP-PRO-CoVLP-021) in participants ≥ 18 years of age.

The Phase 3 portion of Study 021 was a randomized, observer-blind, placebo-controlled study to assess the safety, efficacy and immunogenicity of COVIFENZ in adults 18 years of age or older in North America, South America and Great Britain. The Safety Analysis Set (SAS)

included all randomized participants who received ≥ 1 vaccine or placebo. The SAS was used for unsolicited AE data analysis and comprised 24,076 participants, 12,036 receiving COVIFENZ and 12,040 receiving placebo. Among the participants of 18 to 64 years of age, 11,933 received COVIFENZ and 11,924 the placebo.

Reactogenicity was analyzed in a subset of participants who received both the doses (vaccine or placebo) as per protocol specified regimen and completed 2-month median safety follow-up. For participants 18 to 64 years of age in the safety subset there were 4,094 participants for COVIFENZ and 3,635 participants for the placebo. The participants were monitored for solicited local and systemic reactions after each vaccination with an electronic or paper diary during the 7 days following any dose of vaccination. Participants continued to be monitored for unsolicited adverse events, including serious adverse events, throughout the study.

Solicited local and systemic adverse reactions were reported more frequently among participants in the COVIFENZ group than in the placebo group. The most reported solicited local and systemic adverse reactions in adults 18 to 64 years old, after receiving the first and/or second vaccination were pain at injection site (92.5 %), headache (68.5 %), muscle aches (67.8 %), fatigue (64.7 %), feeling of general discomfort (63.8 %), chills (46.7 %), joint aches (40.0 %), swelling at injection site (38.0 %), swelling in the neck (22.2 %), erythema at injection site (20.1 %), swelling in the axilla (15.1 %) and fever (9.7 %).

In adults 18 to 64 years old, the adverse reactions after vaccination were usually of mild or moderate intensity and resolved within a few days (1 to 3 days). Grade 2 and higher solicited adverse reactions (both local and systemic) were more frequent after the second dose, compared to the first one (see [Table 2](#) and [Table 3](#)).

There were no serious related adverse reactions reported with COVIFENZ, see section [8.2 Clinical Trial Adverse Reactions](#) for more details.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse event and adverse reaction rates observed in clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another vaccine. Adverse events and adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse reactions in real-world use.

Adults 18 to 64 Years of Age

Solicited Adverse Reactions

Solicited adverse reactions were collected from Day 1 to Day 7 after each vaccination and reported by participants in the Safety Subset. [Table 2](#) and [Table 3](#) present the frequency and severity of solicited local and systemic adverse reactions following each dose of COVIFENZ and placebo.

Table 2. Frequency and Severity of Solicited Local Reactions within 7 Days after Each Dose in Adults 18 to 64 Years Old – Phase 3 of Study 021 (Reactogenicity Subset of the Safety Population*, Data cut-off: 25 October 2021)

Local Reaction	Vaccination 1		Vaccination 2	
	COVIFENZ N ^a = 4,094 n ^b (%)	Placebo N ^a = 3,635 n ^b (%)	COVIFENZ N ^a = 4,094 n ^b (%)	Placebo N ^a = 3,635 n ^b (%)
Pain at Injection Site				
Any Grade	3,494 (85.3)	1,080 (29.7)	3,522 (86.0)	1,101 (30.3)
Grade 3 ^{c,e}	22 (0.5)	1 (< 0.1)	29 (0.7)	0
Swelling at Injection Site				
Any Grade	772 (18.9)	107 (2.9)	1,263 (30.9)	113 (3.1)
Grade 3 ^{c,d}	12 (0.3)	1 (< 0.1)	27 (0.7)	0
Erythema at Injection Site				
Any Grade	278 (6.8)	107 (2.9)	646 (15.8)	78 (2.1)
Grade 3 ^{c,d}	7 (0.2)	1 (< 0.1)	41 (1.0)	1 (< 0.1)

* Reactogenicity Subset: All randomized participants who received both the doses (vaccine or placebo) as per protocol specified regimen and completed 2-month median safety follow-up.

^a N = Number of participants in Safety Subset who received vaccination 1 or vaccination 2, respectively.

^b n = Number of participants with the specified reaction.

^c No grade 4 reactions were reported.

^d Erythema and Swelling: Grade 3: > 100 mm / > 10 cm or prevents daily activity

Erythema and Swelling Grade 4: Necrosis/exfoliative dermatitis

^e Pain: Grade 3: Any use of prescription pain reliever / prevents daily activity.

Grade 4: Results in a visit to emergency room (ER) or hospitalization

Table 3. Frequency and Severity of Solicited Systemic Reactions within 7 Days after Each Dose in Adults 18 to 64 Years Old – Phase 3 of Study 021 (Reactogenicity Subset of the Safety Population*, Data cut-off: 25 October 2021)

Systemic Reaction	Vaccination 1		Vaccination 2	
	COVIFENZ N ^a = 4094 n ^b (%)	Placebo N ^a = 3635 n ^b (%)	COVIFENZ N ^a = 4094 n ^b (%)	Placebo N ^a = 3635 n ^b (%)
Headache				
Any Grade	1,640 (40.1)	1,297 (35.7)	2,363 (57.7)	938 (25.8)
Grade 3 ^c	14 (0.3)	10 (0.3)	35 (0.9)	10 (0.3)

Systemic Reaction	Vaccination 1		Vaccination 2	
	COVIFENZ N ^a = 4094 n ^b (%)	Placebo N ^a = 3635 n ^b (%)	COVIFENZ N ^a = 4094 n ^b (%)	Placebo N ^a = 3635 n ^b (%)
Fatigue				
Any Grade	1,484 (36.2)	1,035 (28.5)	2,319 (56.6)	786 (21.6)
Grade 3 ^d	14 (0.3)	12 (0.3)	66 (1.6)	12 (0.3)
Feeling of General Discomfort				
Any Grade	1,196 (29.2)	698 (19.2)	2,323 (56.7)	573 (15.8)
Grade 3 ^e	15 (0.4)	6 (0.2)	37 (0.9)	6 (0.2)
Muscle Aches				
Any Grade	1,758 (42.9)	770 (21.2)	2,306 (56.3)	616 (16.9)
Grade 3 ^d	13 (0.3)	2 (< 0.1)	43 (1.1)	5 (0.1)
Chills				
Any Grade	570 (13.9)	351 (9.7)	1,721 (42.0)	262 (7.2)
Grade 3 ^e	4 (< 0.1)	0	25 (0.6)	1 (< 0.1)
Joint Aches				
Any Grade	640 (15.6)	403 (11.1)	1,384 (33.8)	308 (8.5)
Grade 3 ^e	3 (< 0.1)	3 (< 0.1)	20 (0.5)	1 (< 0.1)
Swelling in the Neck				
Any Grade	474 (11.6)	327 (9.0)	638 (15.6)	244 (6.7)
Grade 3 ^e	2 (< 0.1)	2 (< 0.1)	6 (0.1)	0
Swelling in the Axilla				
Any Grade	264 (6.4)	123 (3.4)	470 (11.5)	70 (1.9)
Grade 3 ^e	1 (< 0.1)	0	2 (< 0.1)	0
Fever				
Any Grade	44 (1.1)	34 (0.9)	361 (8.8)	18 (0.5)
≥39.0 °C – 40.0 °C ^f	3 (< 0.1)	1 (< 0.1)	26 (0.6)	2 (< 0.1)

* Reactogenicity Subset: All randomized participants who received both the doses (vaccine or placebo) as per protocol specified regimen and completed 2-month median safety follow-up.

^a N = Number of participants in the Safety Subset who received vaccination 1 or vaccination 2, respectively.

^b n = Number of participants with the specified reaction.

^c Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

^d Grade 3 fatigue, muscle ache: Defined as significant; prevents daily activity.

^e Grade 3 feeling of general discomfort or uneasiness (malaise), chills, joint ache, swelling in axilla, swelling in the neck: Defined as prevents daily activity and requires medical intervention.

^f Grade 3 fever: ≥39.0 °C – 40.0 °C.

Grade 4 AEs: Defined as requires emergency room visit or hospitalization or for fever grade 4 is defined as > 40.0 °C. All five Grade 4 AEs reported in 5 subjects in the COVIFENZ group. 1 subject with Feeling General Discomfort, 1 subject with Chills, 1 subject with headache, 1 subject with fever and 1 subject with muscle ache.

Unsolicited Adverse Events

As of the cut-off date 25 October 2021, among participants aged 18 to 64 years old who received the first and/or second vaccination of COVIFENZ (11,933 participants) or placebo (11,924 participants) within the Safety Analysis Set, 3,140 (26.3 %) who received COVIFENZ and 2,759 (23.1 %) who received placebo experienced an unsolicited adverse event (includes both non-serious and serious unsolicited AEs).

Serious Adverse Events

As of the cut-off date 25 October 2021, among the participants of 18 to 64 years old, 47 participants (0.4 %) who received COVIFENZ, and 38 participants (0.3 %) who received placebo experienced a serious adverse event.

There were no notable patterns or significant numerical imbalances between treatment groups for specific categories of serious adverse events that would suggest a causal relationship to COVIFENZ.

No deaths or other serious adverse events related to COVIFENZ were reported.

Non-Serious Unsolicited Adverse Events

Unsolicited adverse events that occurred within 21 days following each vaccination are reported below.

Non-serious AEs were reported by 3,121 (26.2 %) who received COVIFENZ and 2,731 (22.9 %) who received placebo, respectively. The most reported non-serious unsolicited adverse events in adults 18 to 64 years old after receiving the first and/or second vaccination in COVIFENZ or placebo group occurring in ≥ 1.0 % of the participants were: headache (4.2 % and 3.8 %, respectively), nasal congestion (2.5 % and 2.3 %, respectively), influenza (2.1 % and 1.9 %, respectively), oropharyngeal pain (1.6 % and 1.7 %, respectively), cough (1.4 % and 1.3 %, respectively), catarrh (1.1 % and 0.9 %, respectively), diarrhea (1.4 % and 1.1 %, respectively), nausea (1.3 % and 0.8 %, respectively), myalgia (1.4 % and 1.0 %, respectively) and influenza-like illness (1.4 % and 1.3 %, respectively). In addition, lymphadenopathy was reported at 0.4 % in the COVIFENZ group and 0.2 % in the placebo group.

There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to COVIFENZ.

Throughout the safety follow-up period, facial paralysis (or Bell's palsy) was reported by 3 participants in the COVIFENZ group and 1 in the placebo group. Onset in the vaccine group participants was from 5 days after dose 1, 13 and 60 days after dose 2, respectively. Onset in the placebo group participants was from 20 days after dose 2. Non-serious cases of pharyngeal swelling were reported by 5 participants in the COVIFENZ group. The onset date was from 0, 8 and 18 days after dose 1, and 18 and 40 days after dose 2, respectively. Available information on facial paralysis (or Bell's palsy) and pharyngeal swelling is insufficient to determine a causal relationship with the vaccine.

Post-Market Adverse Reactions

No post-market data are currently available for COVIFENZ.

9 DRUG INTERACTIONS

No interaction studies have been performed.

Do not mix COVIFENZ antigen or adjuvant components, with other vaccines / products in the same syringe.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

COVIFENZ is an adjuvanted vaccine composed of plant-based virus-like particles (VLP) that closely mimics the native SARS-CoV-2 virus and activates local innate immune responses.

The vaccine then elicits both neutralizing antibody and cellular immune responses to the spike antigen, which may contribute to protection against COVID-19.

11 STORAGE, STABILITY AND DISPOSAL

Storage:

1. Unopened vials must be stored in a refrigerator (2 °C to 8 °C).
2. Do not freeze. If frozen, discard.
3. Check the expiry date on the antigen and adjuvant vials. The shelf-life on outer cartons, containing the antigen and the adjuvant, is based on the component with the shorter expiry date.
4. Once the antigen and adjuvant components are mixed, the vaccine must be used within 6 hours, handled, and stored at room temperature (20 °C to 30 °C). Protect from light. Do not refrigerate. If the vaccine is refrigerated, it must be discarded.
5. Any unused product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

For important information on handling and preparation for administration, see sections **4.3 RECONSTITUTION** and **11 STORAGE, STABILITY AND DISPOSAL**.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Proper name: COVIFENZ, COVID-19 Vaccine (plant-based virus-like particles [VLP], recombinant, adjuvanted)

Other names: Coronavirus-like particles (CoVLP)
Recombinant SARS-CoV-2 spike (S)-protein virus-like particle

ATC Classification: J07BX03

Product Characteristics

COVIFENZ, COVID-19 Vaccine (plant-based virus-like particles [VLP], recombinant, adjuvanted), contains purified, spike protein of SARS-CoV-2 expressed in virus-like particles (VLP) produced by plant-based technology. The production process of COVIFENZ starts with the SARS-CoV-2 genomic sequence of the spike protein from the original strain. The sequence is delivered to host leaf cells of non-transgenic plants using a bacterial vector, via agroinfiltration. The enveloped VLP in COVIFENZ present spike protein trimers of SARS-CoV-2 stabilized in pre-fusion conformation on their surface.

COVIFENZ is supplied as a transparent to opalescent, colourless to yellowish suspension that may contain visible white particulates. No live viruses, egg proteins, preservatives or human-derived materials are used in the formulation and manufacture of the antigen. COVIFENZ is supplied as multidose vials that must be mixed with the sterile AS03 adjuvant before use (see [4.3 RECONSTITUTION](#)).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

COVIFENZ used in clinical trials contains the recombinant SARS-CoV-2 spike (S)-protein, derived from original strain of SARS-CoV-2.

The safety and efficacy of COVIFENZ were evaluated in Study 021, a Phase 2/3 randomized, placebo-controlled, multicentre study in participants 18 years of age and older.

The Phase 2 portion of Study 021 (CP-PRO-CoVLP-021) was a randomized, observer-blind, placebo-controlled, clinical study conducted in Canada and in the United States to evaluate the safety and immunogenicity in adults 18 years of age and older. A total of 753 participants were randomized; 421 participants in the group 18 to 64 years of age, and 332 participants in the group 65 years of age and older received at least one dose of COVIFENZ or placebo and were included in the safety analysis set. Six-hundred and thirty-two (632) participants received COVIFENZ, and 121 participants received placebo.

The Phase 3 portion of Study 021 was an event-driven, randomized, observer-blinded, placebo-controlled study, and was conducted in North America, South America and Great Britain to evaluate the safety, immunogenicity and efficacy in participants 18 years of age and older. The date of the first participant visit was 15 March 2021. The study is still ongoing.

As of the efficacy data cut-off date of 20 August 2021, a total of 24,141 (12,074 in the COVIFENZ group and 12,067 in the placebo group) participants were randomized equally to receive two doses of COVIFENZ or placebo separated by 21 days (19 - 23 days, per study protocol). Among all the randomized subjects, 24,076 subjects (99.7 %) received at least one dose of COVIFENZ or placebo. Of all the subjects, 1,508 subjects (12.5 %) who received the COVIFENZ and 4,567 subjects (37.9 %) who received the placebo discontinued the study prematurely. The per protocol (PP) population comprised 20,090 participants.

Participants with pre-existing stable chronic disease (including but not limited to obesity, documented hypertension, diabetes in $\geq 1\%$ in at least one group), defined as no new onset or exacerbation of pre-existing chronic disease three months prior to vaccination, were included. The study excluded participants who had previous virologically confirmed diagnosis of COVID-19.

The primary endpoint was defined as occurrence of laboratory-confirmed (by RT-PCR) symptomatic SARS-CoV-2 infection (≥ 7 days post-second vaccination). Participants continue to be followed for a period of 12 months after the last vaccination to evaluate the durability of the immune response and safety.

Demographic and baseline characteristics were balanced amongst participants who received COVIFENZ and those who received placebo. In the Per Protocol (PP) population analysis set, for participants who received COVIFENZ, the median age was 29 years (range: 18 to 64 years); 99.4 % (n=9,541) were 18 to 64 years old and 0.6 % (n=55) were aged 65 and older; 50.1% were female aged 18 to 64 years old; in the 18 to 64 years old group 45 % were from the Argentina, 31.8 % from Brazil, 9.3 % from USA, 6.7 % from Mexico, 5.9 % from Canada and 1.2 % from Great Britain; 88.9 % were White, 6.3 % were Black or African American, 1.8 % were from multiple races, 1.2 % were Asian, 0.5 % did not report their race, 0.2 % were American Indian (including Native Americans), 0.2 % were Native Hawaiian or Other Pacific Islander and less than 0.1 % were reported missing or other. At least one pre-existing comorbidity or lifestyle characteristic associated with an increased risk of severe COVID-19 was present in 3,467 (14.4 %) participants. Comorbidities included: Obesity (10.0 %), Documented Hypertension (2.8 %), Type 2 Diabetes (0.9 %), Immunocompromised (0.4 %), Chronic Obstructive Lung Disease (0.4 %), Cardiovascular disease (0.3 %), Asthma (0.2 %).

14.2 Study Results

In the PP population, a total of 157 participants had virologically (RT-PCR) confirmed COVID-19 occurring ≥ 7 days post second dose. There were 39 cases confirmed in the vaccine group and 118 cases confirmed in the placebo group. Based on these cases, vaccine efficacy (VE) was estimated to be 71.0 % (95% CI: 58.7, 80.0), [Table 4](#) below presents the diversity of variants that were identified during the Phase 3 study (March to August 2021).

A total of two participants with their first occurrence of severe COVID-19 occurring ≥ 7 days post second vaccination was documented among all the participants in the PP population, with both participants in the placebo group.

As of 03 December 2021, 114 of the 157 cases (72.6 %) have been sequenced in the PP population. An additional 21 of the 157 cases (13.4 %) could not be amplified to determine the variant sequence. The variants detected in the 114 participants are shown in [Table 4](#).

Table 4. Participants with COVID-19 (≥ 7 days post second vaccination) by Variant (PP population)

Variant (RT-PCR confirmed; per COVID-19 type)	COVIFENZ (N =10,544) ^a n ^b (Attack Rate ^c)	Placebo (N = 9,536) ^a n ^b (Attack Rate ^c)
Any variant (all subjects) ^d	39 (0.4)	118 (1.2)
Original	0	0
Alpha / B.1.1.7	0	5 (< 0.1)
Delta / B.1.617.2	11 (0.1)	39 (0.4)
Gamma / P.1	6 (< 0.1)	46 (0.5)
Lambda / C.37	0	3 (< 0.1)
Mu / B.1.621	0	4 (< 0.1)

Abbreviations: CI = confidence interval, COVID-19 = coronavirus disease 2019; PP = Per Protocol; RT-PCR = Reverse Transcriptase Polymerase Chain Reaction.

^a N = Number of participants in a population.

^b n = Number of participants in categories.

^c Attack Rate = the number of cases as a proportion of number in population; Attack rates represent results up to the date of by-strain analysis and not of the complete population of cases.

^d As of 03 December 2021, 114 of the 157 cases (72.6 %) have been sequenced; and an additional 21 cases could not be amplified to determine the variant sequence.

15. MICROBIOLOGY

No microbiological information is required for this product.

16. NON-CLINICAL TOXICOLOGY

Non-clinical data did not suggest any special hazard of COVIFENZ for humans based on several safety studies, a conventional study of repeat dose toxicity and a reproductive and developmental toxicity study.

General Toxicology:

Intramuscular administration of COVIFENZ at doses ranging from 1 to 10 mcg / dose administered to mice twice (21 days apart) resulted in transient signs of inflammation at the injection site (erythema and edema) and slight body weight changes. In general, all changes resolved within 2 weeks. Increased splenic and more rarely hepatic extramedullary hematopoiesis (correlating with increased spleen weight) were observed and are consistent with an expected immunostimulatory response following intramuscular administration of a vaccine and are therefore not deemed adverse.

Carcinogenicity:

Carcinogenic potential was not assessed, as carcinogenicity studies are not considered relevant to this vaccine.

Genotoxicity:

Genotoxicity potential was not assessed, as genotoxicity studies are not considered relevant to this vaccine.

Reproductive and Developmental Toxicology:

In a developmental and reproductive toxicity study, either placebo or 3 mcg / dose (4 doses) of COVIFENZ were intramuscularly administered to female rats 22 and 8 days prior to cohabitation for mating and on gestational day (GD) 6 and GD19. IM administration of COVIFENZ elicited detectable anti-SARS-CoV-2 S-glycoprotein maternal antibodies in dams that were detected in fetuses and pups. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

COVIFENZ®

COVID-19 Vaccine (Plant-based virus-like particles [VLP], recombinant, adjuvanted), Emulsion for intramuscular injection

This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about COVIFENZ.

What is COVIFENZ used for?

COVIFENZ is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus.

COVIFENZ can be given to people from 18 to 64 years of age.

How does COVIFENZ work?

COVIFENZ works by helping your body to protect itself against COVID-19 by producing both antibodies and immune cells that recognize the virus, helping to prevent you from getting COVID-19 entirely or limiting how sick you become.

COVIFENZ is made of proteins in the form of Virus-Like Particles (VLP) from plants that produce these particles. The VLP in COVIFENZ looks like the SARS-CoV-2 virus to your immune system. COVIFENZ does not contain the virus that causes COVID-19 so you cannot catch COVID-19 from this vaccine.

As with any vaccine, COVIFENZ may not fully protect all those who receive it. Even after you have had both doses of the vaccine, continue to follow the recommendations of local public health officials to prevent spread of COVID-19.

What are the ingredients in COVIFENZ?

Medicinal ingredient: Virus-Like Particles (made in plants).

Non-medicinal ingredients:

- Polysorbate 80
- Potassium Phosphate Monobasic Anhydrous
- Sodium Chloride
- Sodium Phosphate Dibasic Anhydrous
- Water for Injection.

May contain trace amounts of polyethylene glycol, kanamycin and carbenicillin.

The AS03 adjuvant used with COVIFENZ makes the immune response stronger and contains naturally occurring molecules (squalene and vitamin E) plus an emulsifier (polysorbate 80) and phosphate buffered saline. The vaccine does not contain any live viruses, egg proteins, preservatives, or human-derived materials.

COVIFENZ comes in the following dosage form:

The mixed vaccine is a whitish to yellowish homogeneous milky liquid emulsion in a multidose vial. Each dose is 0.5 mL and contains 0.25 mL (3.75 mcg) of virus-like particles (VLP) SARS-CoV-2 spike protein, adjuvanted with 0.25 mL of AS03.

You should not receive COVIFENZ if:

- you are allergic to any of the ingredients in this vaccine (see **What are the ingredients in COVIFENZ?**)
- you had an allergic reaction after a previous dose of this vaccine
- you have any symptoms that could be due to COVID-19. Talk with your healthcare professional about your symptoms and getting a COVID-19 test. Your healthcare professional will advise you when you are able to receive the vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive COVIFENZ. Talk about any health conditions or problems you may have, including if you:

- have had any problems following previous administration of COVIFENZ such as an allergic reaction or breathing problems
- have any other allergies
- have a weakened immune system due to a medical condition or are on a medicine that affects your immune system
- are feeling nervous about the vaccination process or have ever fainted in association with an injection
- have a bleeding problem, bruise easily or use a blood thinning medication
- are pregnant, think you may be pregnant, or plan to become pregnant
- are breastfeeding.

Other warnings you should know about:

It may take at least 7 days after the second dose of COVIFENZ to develop an optimal protection against COVID-19. As with any vaccine, COVIFENZ may not fully protect all those who receive it.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

There is no information on the use of COVIFENZ with other vaccines.

Tell your healthcare professional if you have recently received any other vaccine.

How COVIFENZ is given:

Usual dose:

COVIFENZ is given as an injection of 0.5 mL into a muscle of your upper arm.

You will receive 2 injections, given 21 days apart. It is very important that you return for the second injection, or the vaccine may not work as well. If you have received a first dose of COVIFENZ, you should receive COVIFENZ as a second dose to complete the vaccination series.

If you have any further questions on the use of COVIFENZ, ask your healthcare professional.

Overdose:

In the event of suspected overdose with COVIFENZ, contact your regional poison control centre.

Missed Dose:

If you forget to go back to your healthcare professional at the scheduled time for your next dose, ask your healthcare professional for advice.

What are possible side effects from using COVIFENZ?

Like all vaccines, COVIFENZ may cause side effects, although not everybody gets them.

The following are common or very common side effects. Most of these side effects are mild and do not last long. Tell your doctor if you have side effects that bother you:

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

- injection site pain, swelling, redness
- headache
- fatigue (feeling tired)
- generally feeling unwell or uneasy
- muscle or joint aches / pain
- chills
- joint aches/pain
- swelling in the neck
- swelling in the armpit

Common (may affect more than 1 in 100 people and up to 1 in 10 people)

- fever

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

Your vaccination provider may ask you to stay at the place where you received your vaccine for at least 15 minutes to 30 minutes for monitoring.

Should you develop any serious symptoms or symptoms that could be an allergic reaction, seek medical attention right away. Symptoms of an allergic reaction may include:

- hives (bumps on the skin that are often very itchy)
- swelling of the face, tongue, or throat
- difficulty breathing
- a fast heartbeat
- dizziness and weakness

There is a remote chance that COVIFENZ could cause an allergic reaction. If you experience a severe allergic reaction, call 9-1-1 or go to the nearest hospital.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Medicago Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (<https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html>) and send it to your local Health Unit.

Storage:

COVIFENZ should be stored, supplied, and administered by a healthcare professional. Keep out of reach and sight of children.

If you want more information about COVIFENZ:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>), the manufacturer's website www.COVIDVLP.com, or by calling 1-800-622-6067.
- The Patient Medication Information is also available by scanning the QR code on the label.

This leaflet was prepared by Medicago Inc.



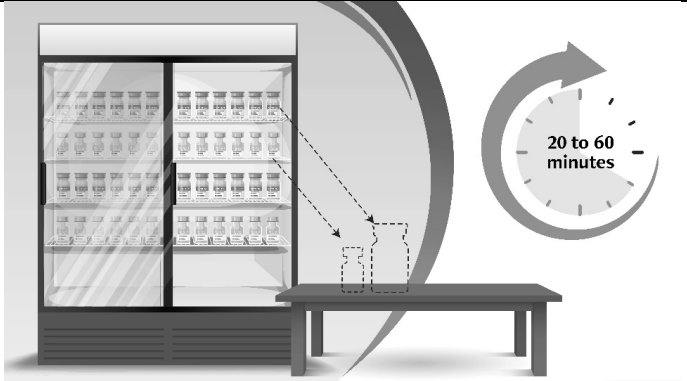
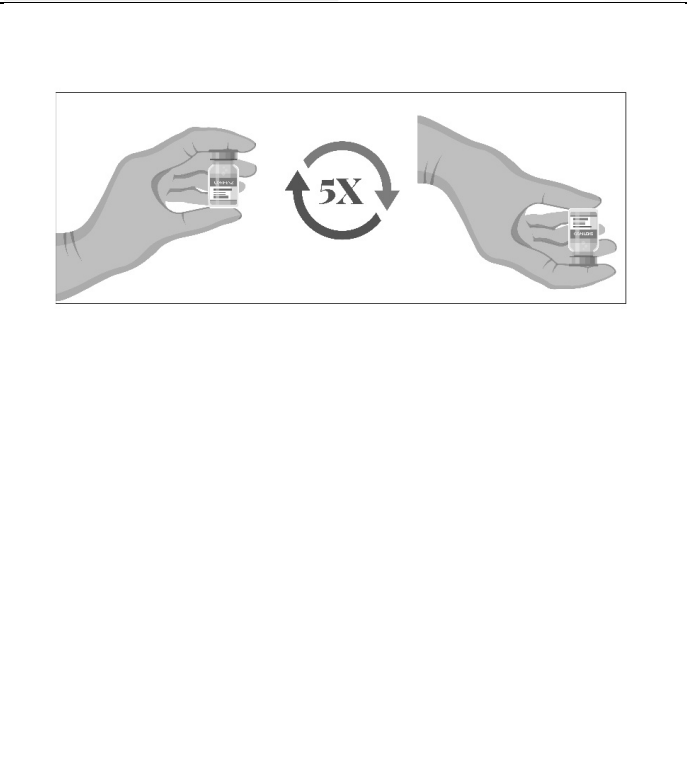
Last Revised: February 24, 2022


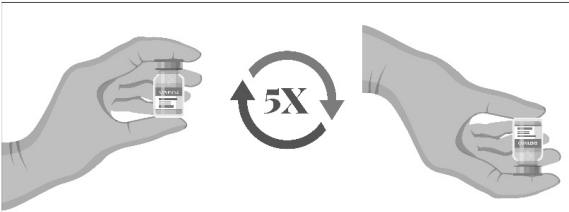

Instructions for Use

The following information is intended for healthcare professionals only:

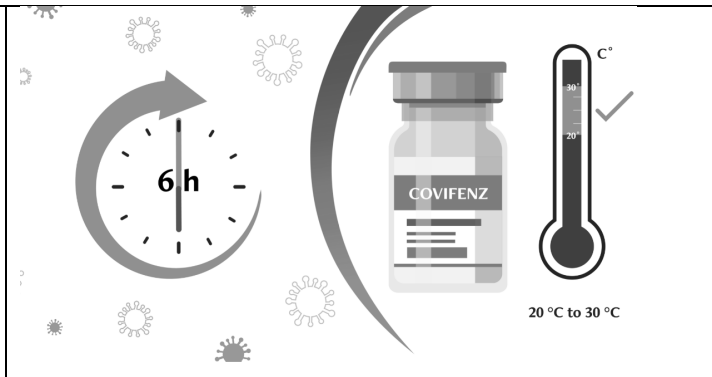
Preparation for Administration:

Check the expiry date on the antigen and adjuvant vials. Mixing of the COVIFENZ antigen with the adjuvant is required prior to administration.

Prior to mixing	
<p>1. Remove the antigen and adjuvant vials from the refrigerator and allow them to reach room temperature (no less than 20 minutes, no more than 60 minutes).</p>	
<p>2. Gently invert each vial 5 times or until homogeneity is obtained. <u>Do not vortex or mix vigorously (no shaking).</u></p> <p>3. Inspect the antigen and AS03 adjuvant vials for foreign matter, change in colour and / or leakage prior to mixing. If one of these conditions exist, the antigen or AS03 adjuvant vial must be discarded.</p> <ul style="list-style-type: none">• Antigen content should be transparent to opalescent, colorless to yellowish liquid suspension. It may contain visible white particulates.• AS03 adjuvant content should be whitish to yellowish homogenous milky liquid emulsion.	

Mixing	
<p>4. Strict adherence to aseptic techniques must be followed.</p> <p>5. Hold and keep the adjuvant vial upside down. Use a 5 mL syringe (at least 21- gauge needle) to fully withdraw the entire content of the adjuvant vial and transfer it to the larger antigen vial.</p> <p>6. Do not mix COVIFENZ with other vaccines / products in the same syringe.</p>	
<p>7. Gently invert the vial containing the mixed content a minimum of 5 times or until homogeneity is obtained. <u>Do not shake vials or mix vigorously.</u></p> <p>The concentration of the mixed vaccine, an emulsion for injection is 7.5 mcg / mL.</p> <p>8. Prior to use, inspect for foreign matter, change in colour and/or leakage. If one of these conditions exists, the vaccine must not be used.</p> <ul style="list-style-type: none"> • The mixed vaccine should be a whitish to yellowish homogeneous milky liquid emulsion; otherwise, it must be discarded. 	
<p>9. Record the time that the components were mixed on the antigen vial label.</p>	

10. The vaccine must be used within 6 hours and stored at room temperature (20 °C to 30 °C) until administered. Do not refrigerate. Protect from light.



Administration

1. Before every administration, gently invert the vial until homogeneity is obtained.
2. Inspect for foreign matter, change in colour and/or leakage. If any of these conditions exists, the vaccine must not be administered.
3. Cleanse the vial stopper with a single-use antiseptic swab, allow to dry.
4. It is recommended to use a 1 mL syringe with a 23-gauge needle for vaccine withdrawal and injection.
5. Choose needle length based on the patient weight. Ensure that the needle is tightly attached to the syringe.
6. Withdraw a dose (0.5 mL) and administer into the deltoid muscle.

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