SUMMARY OF PRODUCT CHARACTERISTICS

GCFLU Quadrivalent Pre-filled Syringe inj.

GC Biopharma Corp.

* The Summary of Product Characteristics (SmPC) has been structured in accordance with Article 11 of Directive 2001/83/EC, and the presented information is pertinent to the Korean Licensure of the product.

1. NAME OF THE MEDICINAL PRODUCT

GCFLU Quadrivalent Pre-filled Syringe inj.

2. QUANTITATIVE AND QUANTITATIVE COMPOSITION

1 pre-filled syringe 0.5 mL contains,

Purified Inactivated Influenza Virus Antigen Type A [A/Victoria/4897/2022 IVR-238 (H1N1)]	15 µg
Purified Inactivated Influenza Virus Antigen Type A [A/Darwin/9/2021 SAN-010 (H3N2)]	15 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Austria/1359417/2021 BVR-26]	15 µg
Purified Inactivated Influenza Virus Antigen Type B [B/Phuket/3073/2013]	15 µg
Sodium chloride	4 mg
Potassium chloride	0.1 mg
Disodium hydrogen phosphate dihydrate	0.6 mg
Potassium dihydrogen phosphate	0.1 mg
Water for injection	q.s.

This vaccine complies with the WHO recommendations (Northern Hemisphere) for 2023-2024 season.

3. PHARMACEUTICAL FORM

Pre-filled syringe containing colorless or slightly whitish liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis against influenza caused by influenza A subtype viruses and type B viruses in persons aged 6 months and older.

4.2 Posology and Method of Administration

An intramuscular injection of the following dose and immunization of one dose is necessary in every year at same volume.
Aged 6 months and older: A single dose of 0.5 mL
The children younger than 9 years of age who have not been vaccinated should be vaccinated two doses at an interval of at least 4 weeks.
The preferred sites for intramuscular injection are the anterolateral aspect of the thigh (or the deltoid muscle of the upper arm if muscle mass is adequate) in children 6 through 35 months of age, or the deltoid muscle of the upper arm in children from 36 months of age and adults.

The safety and efficacy of the vaccine was not established in children younger than 6 months.

4.3 Contraindications

Examine subjects by history taking and visual inspection and if necessary, by auscultation and percussion. Vaccination is prohibited when subject is diagnosed as one of the following cases. However, if it is seems to be infected with influenza and determined that there is no concern for disabilities due to vaccination, vaccination may be permitted.

1) Febrile patient or person with malnutrition.
2) Patients with cardiovascular disorders, kidney disorders, or liver disease in which the disease is in acute phase, stadium increment, or in active phase.
3) Patients with acute respiratory disease or other active infectious disease.
4) Patients in latent and convalescence period.
5) Person who showed anaphylaxis by the components of the product.
6) Person with hypersensitivity to egg, chicken, any other chicken component, and the product component.
7) Person who had fever within 2 days or a symptom of allergy such as generalized rash after the injection at previous vaccination.
8) Person who showed the symptom of convulsion within 1 year before vaccination.
9) Person who showed Guillain-Barre syndrome or person with neurological disorders within 6 weeks from the previous influenza vaccination.
10) Person diagnosed with immunodeficiency disease.
11) Person in inappropriate condition to be vaccinated.

4.4 Special Warnings and Precautions for Use

4.4.1 General precautions

1) Advise the subjects or their guardians that the subjects should keep equilibrium, keep the injection site clean, and when the symptoms of high fever, convulsion appear, they should consult a physician quickly.
2) Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.
3) Influenza vaccine should be administered before prevailing. Vaccination can be delayed according to epidemiological situation.
4) Influenza vaccine should be administered with current-year recommended strains.

4.5 Interaction with other medicinal products and other forms of interaction

1) There is no data or study on co-administration of this product with other vaccines.

2) The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

3) Following influenza vaccination, false positive results in serologic tests using the ELISA method to detect antibodies against HIV-1, Hepatitis C, and especially HTLV-1 have been observed (The Western Blot technique disproves the false-positive ELISA test results). These transient false-positive results could be due to the IgM response by the vaccine.

4.6 Pregnancy and Nursing Mothers

Pregnancy

- Inactivated Influenza vaccine (egg-derived) is known that it can be used in all pregnancy cycles regardless of the pregnancy stage. There are more safety data for second trimester and third trimester compared with the first trimester. In addition, according to data on the usage of inactivated influenza vaccine collected globally, no adverse effects of the vaccine on the fetus and maternity were reported.

- In addition, no direct or indirect adverse effects related to reproductive toxicity and developmental toxicity were observed in animal studies conducted using this vaccine. However, clinical trials have not evaluated the safety of the pregnant women when administered this vaccine.

Nursing Mothers

- Inactivated Influenza vaccine (egg-derived) is known that it can be used to lactating women. Restricted data indicate that the vaccine is not known whether the product is excreted in human milk. However, there is no adequate study of vaccination in animals during lactation, and clinical trials have not evaluated the safety of nursing mothers when administered this vaccine.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section 4.8 “Undesirable Effects” may affect the ability to drive or use machines.

4.8 Undesirable Effects

1) There is possibility of local reactions such as redness, swelling and pain, or systemic reactions such as fever, chills, headache, fatigue and vomiting. But they usually disappear within 2-3 days.
2) In rare cases, acute disseminated encephalomyelitis (ADEM) may occur.
   Fever, headache, convulsions, dyskinesia and consciousness disorder usually occur within 2 weeks following the administration of the vaccine. When these symptoms are suspected, appropriate medical treatment should be available by diagnosis with MRI and so on.
3) Allergic reaction or anaphylactic shock may occur in very rare cases.
4) Transient disorders of systemic and local nervous system may rarely occur. Palsy, neuralgia, cerebral hemorrhage or inflammation of the nervous system (ex: Guillain-Barre syndrome) have been reported.
5) Safety of the vaccine was evaluated for the 4 clinical studies performed with healthy children, adults, and elderly.

In children aged 6 through 35 months who received the vaccine, 115 subjects (67.6%) out of 170 subjects showed adverse events. Adverse drug reactions were 82 subjects (48.2%) and no serious adverse drug reactions were reported. In children aged 3 through 18 years who received the vaccine, 218 subjects (68.3%) out of 319 subjects showed adverse events. Adverse drug reactions were 204 subjects (63.9%) and no serious adverse drug reactions were reported.
In adults aged 19 through 64 years who received the vaccine, 415 subjects (71.2%) out of 583 subjects showed adverse events. Adverse drug reactions were 399 subjects (68.4%) and no serious adverse drug reactions were reported.
In elderly over 65 years of age who received the vaccine, 148 subjects (43.8%) out of 338 subjects showed adverse events. Adverse drug reactions were 140 subjects (41.4%) and no serious adverse drug reactions were reported.

(1) Solicited adverse drug reactions within 7 days of vaccination are listed in the table below.

		Children aged 6 through 35 months (n=170)	Children aged 3 through 18 years (n=319)	Adults aged 19 through 64 years (n=583)	Elderly over 65 years of age (n=338)
Local	Pain	27.6%	52.7%	48.9%	21.0%
	Tenderness		54.5%	56.8%	27.5%
	Erythema/Redness	11.8%	6.6%	7.9%	3.8%
	Induration/Swelling	5.9%	8.2%	5.8%	3.6%
Systemic	Drowsiness[1)]	15.9%	-	-	-
	Fever	6.5%	3.1%	0.9%	0.3%
	Sweating	2.4%	2.2%	4.3%	2.7%
	Chills	2.4%	5.0%	7.7%	4.4%
	Nausea/Vomiting	2.4%	0.6%	2.2%	0.9%
	Diarrhea	5.9%	0.3%	1.5%	1.2%
	Fatigue	-	15.4%	25.6%	10.7%
	Malaise	-	11.0%	7.5%	8.3%
	Headache	0.6%	6.9%	13.4%	7.1%
	Muscle aches	7.6%	8.2%	26.4%	6.5%
	Arthralgia	-	1.6%	5.8%	3.6%

1) Drowsiness only applies for children and 6 months through 35 months

(2) Unsolicited adverse drug reactions occurring within 28 days or 21 days of vaccination were reported in 4 subjects (2.4%) from children aged 6 through 35 months (Infections and infestations: 3 subjects, Skin and subcutaneous tissue disorders: 1 subject), 3 subjects (0.9%) from children aged 3 through 18 years (General disorders and administration site conditions: 2 subjects, Infections and infestations: 1 subject), 13 subjects (2.2%) from adults (Infections and infestations: 5 subjects, investigations: 2 subjects, Respiratory thoracic and mediastinal disorders: 2 subjects, Musculoskeletal and connective tissue disorders: 1 subject, Nervous system disorders: 1 subject, Skin and subcutaneous tissue disorders: 1 subject, General disorders and administration site conditions: 2 subjects), and 4 subjects (1.2%) from elderly (Infections and infestations: 1 subject, General disorders and administration site conditions: 1 subject, investigations: 1 subject, Nervous system disorders: 1 subject)

(3) Serious adverse events occurring within 6 months of vaccination were reported in 13

subjects (7.6%) from children aged 6 through 35 months (Pneumonia: 4 cases, Influenza: 3 cases , Bronchitis: 2 cases , Pneumonia respiratory syncytial viral: 1 case, Bronchiolitis: 1 case, Croup infectious: 1 case, Gastroenteritis norovirus: 1 case, Gastroenteritis rotavirus: 1 case, Urinary tract infection: 1 case, Gastrointestinal infection: 1 case, Impaired healing: 1 case, Foreign body in gastrointestinal tract: 1 case, Febrile convulsion: 1 case), 5 subjects (1.6%) from children aged 3 through 18 years (Pharyngitis: 1 case, Headache: 1 case, Mesenteric lymphadenitis: 1 case, Acute gastroenteritis: 1 case, Peritonsillar Abscess: 1 case, Acute appendicitis: 1 case), 5 subjects (0.9%) from adults (Cystitis: 1 case, Pulmonary Tuberculosis: 1 case, Breast mass: 1 case, Ileus : 1 case, Gastric cancer: 1 case), and 4 subjects (1.2%) from elderly (Pain: 1 case, Arthralgia: 1 case, Herpes zoster: 1 case, Gastric cancer: 1 case), but they were evaluated as 'not related' to the product.

6) Results of post-marketing surveillance in South Korea

(1) The results of post-marketing surveillance conducted domestically for 4 years on 2,060 adult subjects aged 19 years and older in order to go through a re-examination showed that the incidence of adverse events was 10.49% (216 out of 2,060 subjects, 578 cases in total), regardless of causal relationship.

Among these, no serious adverse events and serious adverse drug reactions have been reported.

In addition, unexpected adverse events and unexpected adverse drug reactions are listed in the following table according to their frequency of onset.

		Unexpected Adverse Events Regardless of Causal Relationship 2.33% (48 out of 2,060 subjects, 72 cases)	Unexpected Adverse Drug Reactions of Which Causal Relationship Cannot Be Ruled Out 0.29% (6 out of 2,060 subjects, 7 cases)
Rarely (≥ 0.01% and < 0.1%)	Respiratory, thoracic, and mediastinal disorders	Asthma	Cough
	Gastrointestinal disorders	Dyspepsia, benign gastrointestinal neoplasm, gastrointestinal disorder NOS, hemorrhoids	-
	General disorders and administration site condition	Injection site inflammation	Injection site inflammation
	Nervous system disorders	Apathy, insomnia, dizziness, cerebral ischemia	Apathy, dizziness
	Eye disorders	Blepharitis, conjunctivitis	-
	General disorders and administration site condition	Back pain	-

	Vascular disorders	Hypertension	-
	Cardiac disorders	Palpitation	Palpitation
	Metabolism and nutrition disorders	Hyperlipidemia	-
	Infections and infestations	Fungal dermatitis, moniliasis	-
Uncommonly (≥ 0.1% and < 1%)	Respiratory, thoracic, and mediastinal disorders	Rhinitis, sinusitis, cough, upper respiratory tract infection	-
	Gastrointestinal disorders	Gastritis, gastroesophageal reflux, abdominal pain, irritable bowel syndrome	-
	Skin and subcutaneous tissue disorders	Dermatitis, pustular rash, contact dermatitis, urticaria	-
	General disorders and administration site condition	Cellulitis, injection site pruritus	Injection site pruritus

(2) The results of post-marketing surveillance conducted domestically for 4 years on 2,033 pediatric subjects aged ≥ postnatal 6 months and < 19 years showed that the incidence of adverse events was 30.74% (625 out of 2,033 subjects, 1,221 cases in total), regardless of causal relationship. Among these, serious adverse events and serious adverse drug reactions are listed in the following table according to their frequency of onset.

		Serious Adverse Events 0.10% (2 out of 2,033 subjects; 2 cases)	Serious Adverse Drug Reactions 0.00% (0 out of 2,033 subjects; 0 cases)
Rarely (≥ 0.01% and < 0.1%)	White cell and reticuloendothelial system disorders	Kawasaki disease*	-
	Respiratory system disorders	Bronchitis	-

* Unexpected serious adverse event

In addition, unexpected adverse events and unexpected adverse drug reactions are listed in the following table according to their frequency of onset.

	Unexpected Adverse Events Regardless of Causal Relationship	Unexpected Adverse Drug Reactions of Which Causal Relationship Cannot Be Ruled Out

		7.82% (159 out of 2,033 subjects; 178 cases)	0.49% (10 out of 2,033 subjects, 10 cases)
Rarely (≥ 0.01% and < 0.1%)	Application site disorders	Cellulitis, Injection site bruising	Injection site bruising
	Body as a whole-general disorders	Leg pain, Influenza-like symptoms, Hypothermia, Temperature changed sensation	Leg pain, Hypothermia, Temperature changed sensation
	Gastrointestinal system disorders	Constipation, Gastroesophageal reflux	-
	Skin and appendages disorders	Acne, Dermatitis contact, Dermatitis fungal, Skin disorder	Rash pustular
	Resistance mechanism disorders	Moniliasis	Otitis media
	White cell and reticuloendothelial system disorders	Kawasaki disease, Lymphadenopathy	-
	Secondary terms - events	Varicella	-
Uncommonly (≥ 0.1% and < 1%)	Respiratory system disorders	Sinusitis, Cough, Asthma	-
	Application site disorders	Injection site pruritus	Injection site pruritus
	Gastrointestinal system disorders	Abdominal pain, Stomatitis	-
	Skin and appendages disorders	Dermatitis, Rash pustular, Urticaria, Pruritus	Urticaria
	Resistance mechanism disorders	Otitis media	-
	Vision disorders	Conjunctivitis	-
Commonly (≥ 1% and < 10%)	Respiratory system disorders	Rhinitis	-

(3) Adverse events from domestic post-marketing surveillance and spontaneously reported data on side effects were comprehensively assessed at the end of post-marketing surveillance along with the adverse events data (1989 to December 31, 2020) reported for all drugs that have been licensed for domestic marketing. Among the adverse events that were reported more frequently with statistical significance for this drug than the adverse events reported

for all other drugs, following adverse events were newly identified. However, these results do not mean that the causal relationship between the relevant ingredient and the following adverse events has been demonstrated.

- Systemic and injection site adverse events: Injection site inflammation, injection site warmth, injection site pruritus, injection site bruising
- Infection: Rhinitis (rhinorrhea)

4.9 Overdose

Cases of administration of more than the recommended dose (overdose) have not been reported with this product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

Efficacy(Immunogenicity) of GCFLU Quadrivalent Pre-filled syringe('GC3110A')

A total of 45 clinical trials were conducted to assess the efficacy (immunogenicity) of 'GC3110A', and of these, two were targeted at adults, and the total number of subjects who received injection of investigational products was 1,865. The total number of subjects who received injection of investigational products was 542 in one clinical trial in children, and the total number of subjects who received injection of investigational products was 209 in one clinical trial in infants. From clinical trial conducted to assess the efficacy (immunogenicity) of GC3110A, the following conclusions were made:

- After injection of investigational products into subjects of age 19 and older, HI antibody-titers were measured and GMT and SCR results revealed that GC3110A is not inferior to GC FLU Prefilled Syringe Inj. and GC3110A (control drug).
- When compared to GC FLU Prefilled Syringe Inj. and GC3110A (control drug) which contain one of two strain B antigens (Yamagata and Victoria), GC3110A containing both strain B antigens showed more effective immunological responses against such additional strain B antigen in terms of SCR, SPR, GMT and GMT ratio (before and after injection) injection), in subjects aged >19 years.
- Also, subjects aged 6 months to < 19 years showed immune reactions, where GC3110A met the FDA criteria by checking the seroconversion rate (SCR) and seroprotection rate(SPR) per 4 strains through HI antibody test
- Subjects aged 65 years also showed immune reactions, where 'GC3110A' satisfied the FDA criteria by checking the seroconversion rate (SCR) and seroprotection rate (SPR) per 4 strains through HI antibody test.
- In addition, subjects aged 6 months to <3 years showed that 'GC3110A' had immunogenicity satisfying the FDA criteria by checking the seroconversion rate (SCR) and seroprotection rate (SPR) per 4 strains through HI antibody test
- In conclusion, when compared to trivalent influenza split vaccine, which contains only one strain B antigen, the quadrivalent influenza vaccine, GC3110A, which contain both strain B antigens is considered to be more effective in prevention of influenza virus.

Safety of GCFLU Quadrivalent Pre-filled syringe('GC3110A')

In phase 1/2a clinical trial in adults, phase 3 clinical trial in adults, phase 3 clinical trial in children, phase 3 clinical trial in the elderly and phase 3 clinical trial in infants which were conducted in Korea, adverse events incurred in 1,382 healthy adults aged 19 years and older (test drug: 707 subjects, control drug 1: 349 subjects, control drug 2: 326 subjects), 542 healthy children and adolescents aged ≥ 6 months ~ < 19 years (test drug: 438 subjects , control drug: 104 subjects), healthy elderly subjects aged ≥ 65 years (test drug: 274 subjects), and 209 healthy infants aged ≥ 6 months to < 3 years (test drug: 170 subjects, control drug: 39 subjects) were analyzed, and vital signs, physical examination, and laboratory test (only for a clinical trial in adults) were conducted for safety evaluation. From clinical trials conducted to assess the safety of GC3110A, the following conclusions were made:

- For the incidence rate of adverse events in test group (GC3110A), solicited local adverse events, solicited systemic adverse events and unsolicited adverse events were found in this descending order of incidence rates and most adverse events were "Grade 1" or "Grade 2".
- The adverse events with high incidence rates in test group (GC3110A) were 'tenderness', 'pain', 'myalgia', 'fatigue', and 'headache' in phase 1/2a and phase 3 clinical trials in adults. Similarly, in test group (GC3110A) in phase 3 clinical trial in children, and in phase 3 clinical trial in the elderly, the incidence rate of 'tenderness', 'pain', 'fatigue(drowsiness)', and 'malaise' was high and in Part 2 in phase 3 clinical trial in infants, the incidence rate of 'pain/tenderness', 'drowsiness' and 'erythema/redness' was high. Most of the adverse events incurred were mild or moderate.
- In phase 3 clinical trial in adults, when compared to control group (GC FLU Prefilled Syringe Inj.) and GC3110A, test group (GC3110A) showed similar incidence rates of solicited systemic and unsolicited adverse events to control group.

5.2 Pharmacokinetic properties

Not applicable

5.3 Non-clinical safety data

Repeat dose toxicity study (including local tolerance test) and reproductive/developmental toxicity study were conducted in compliance with GLP requirements. Any drug-related adverse effect was not observed in the studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride
Potassium chloride
Disodium hydrogen phosphate dihydrate
Potassium dihydrogen phosphate
Water for injection

6.2 Incompatibilities

Incompatibilities with other drugs have not been evaluated.

6.3 Shelf-life
12 months from the date of manufacture.

6.4 Special precautions for storage
Store at 2-8°C without freezing in hermetic container and protect from light.

6.5 Nature and contents of container
0.5 mL pre-filled syringe x In-house packing unit
(With attached sterilized disposable needle)

6.6 Special precautions for disposal and other handling

1) Before use check this product visually for particles or discoloration. If either is present, do not use.
2) The injection site is usually lateral upper arm and disinfected with ethanol or tincture of iodine. Repeated injections at the same site should be avoided.
3) Intravenous administration is prohibited.
4) The tip of needle should not penetrate blood vessel.
5) Do not mix with other vaccines in same syringe.
6) The vaccine should be shaken well and mixed homogeneously before use
7) Pre-filled syringes are disposable and should not be reused.

7. MARKETING AUTHORISATION HOLDER
GC Biopharma Corp.
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8. MARKETING AUTHORISATION NUMBER(S)
5035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26 Nov 2015

10. DATE OF REVISION OF THE TEXT
10 May 2023