Registration No. 2C 12/66 (NB)

Importer / Manufacturer: Bionovel Co.,Ltd./ SK Bioscience Co., Ltd.

FFA02AF01

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SKYCellflu Quadrivalent prefilled syringe
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)
(2023-2024 season)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (hemagglutinin and neuraminidase)*, inactivated, of the following strains:
[A/Victoria/4897/2022, IVR-238 (H1N1)]……..15 µg HA**
[A/Darwin/9/2021, IVR-228 (H3N2)]……..15 µg HA**
[B/Michigan/01/2021] ……..15 µg HA**
[B/Phuket/3073/2013] ……..15 µg HA**
per 0.5 mL dose

*propagated in Madin Darby Canine Kidney (MDCK) cells
**hemagglutinin
The vaccine complies with the WHO recommendation (northern hemisphere) for the 2023-2024 season.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear or slightly opalescent liquid contained within colorless and transparent prefilled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine, for adults and children 6 months of age and older.
The use of SKYCellflu Quadrivalent should be based on official recommendations.

4.2 Posology and method of administration

Posology
Adults and children 6 months of age and older: 0.5 mL as a single injection.
For children below 9 years of age who have not been previously vaccinated or infected, a second dose should be administered after an interval of at least 4 weeks.

Method of administration
Administration should be carried out by intramuscular injection. The sites of intramuscular injection are the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in children 6 months through 35 months of age, or the deltoid muscle of the upper arm in children from 36 months of age and adults.

4.3 Contrainidications

If deemed necessary after a medical interview and visual inspection, examine the subject's health condition further using methods such as auscultation and percussion. Do not administer the vaccine to subjects with following conditions. As an exception, the vaccine may be administered to subjects who are at risk of possible influenza infection and determined to have no likelihood of developing serious disabilities due to the administration of the vaccine.

1) Hypersensitivity reaction to active ingredient and/or any other ingredient (including formalin) in SKYCellflu Quadrivalent
2) Febrile disease or acute infection
3) History of severe hypersensitivity reaction and/or convulsive symptom to previous influenza vaccination
4) History of Guillain-Barre syndrome or other neurological disorder within 6 weeks of previous influenza vaccination
5) Fever
6) History of anaphylaxis reaction to any ingredient in SKYCellflu Quadrivalent
7) History of suspected allergic reaction, including systemic rash, to previous vaccination
8) Other medical conditions that are diagnosed to be inappropriate for administration of SKYCellflu Quadrivalent vaccine.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

As with other intramuscular injection, patients with bleeding disorder such as hemophilia and thrombocytopenia or patients on anticoagulant therapy should not receive SKYCellflu Quadrivalent unless the potential benefit outweighs the risk of administration. If the decision is made to administer SKYCellflu Quadrivalent in such persons, it should be administered with caution to avoid the risk of hematoma formation following injection.

4.5 Interaction with other medicinal products and other forms of interaction

1) Concurrent immunosuppressive therapy or immunodeficiency may affect immunological response to the vaccine.
2) Co-administration of SKYCellflu Quadrivalent with other vaccine has not been studied. If concomitant vaccination cannot be avoided, injections should be administered on different sites, and the patients should be informed of possible increases in the severity of the adverse effects due to the co-administration.
3) False positive response has been reported from the serum test after influenza vaccination which measures antibody against HIV1, HCV, and particularly HTLV1 using ELISA assay (false positivity confirmed with Western Blot technique). Such temporary false positive result is attributed to IgM reaction from vaccination.
4) Immunosuppressive therapy (radiotherapy, anti-metabolic agent, alkylating agent, cytotoxic agent, and supraphysiological doses of corticosteroid) may reduce the immunological response to influenza vaccine.

4.6 Fertility, pregnancy and lactation

The safety of SKYCellflu Quadrivalent in pregnant women and breast-feeding women has not been assessed in clinical trials.

Pregnant women
Direct and/or indirect adverse effect related to reproduction and developmental toxicity was not observed in animal studies. Because of the consequences of influenza infection in pregnant women, WHO recommends vaccination of pregnant women.

Breast-feeding women
Since it is not known whether SKYCellflu Quadrivalent is excreted in breast milk, caution should be exercised when SKYCellflu Quadrivalent is administered to a nursing mother.

Fertility
No human fertility data are available. Animal data have not shown effects on female fertility. Male fertility has not been assessed in animals.

4.7 Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile
The safety of SKYCellflu Quadrivalent was assessed through phase I/II clinical trial and three phase III clinical trials. Four human clinical studies have been performed with SKYCellflu Quadrivalent and the safety was evaluated in the Safety Analysis Set of 1,506 subjects who were enrolled and received the vaccination with SKYCellflu Quadrivalent. Of 1,506 subjects who received the SKYCellflu Quadrivalent, and 449 healthy infant subjects, 255 healthy pediatric subjects and 802 healthy adult subjects received 0.5 mL. Safety evaluations were performed for all subjects during the first 3 weeks for adults or 4 weeks for pediatric subjects, 6 months to 18 years of age following vaccination. SAEs have been collected during six months of follow-up, except 449 subjects aged 6 through 35 months for whom SAE has been collected 1 month after vaccination.

Summary of adverse reactions
1) Local reaction: adverse reactions including injection site tenderness, pain, erythema/redness, and induration/swelling may occur; these reactions usually disappear instantly.
2) Systemic reaction: systemic reactions including myalgia, fatigue/malaise, headache, diarrhea, and vomiting may occur after vaccination; these reactions usually disappear within 3-4 days.
3) Encephalomyelitis: rarely, acute disseminated encephalomyelitis (ADEM) is reported. Fever, headache, convulsion, motor disorder, cognitive disorder, etc. may occur generally within 2 weeks after vaccination. In a case of suspected ADEM, diagnosis with MRI and proper intervention should be instituted.
4) Very rarely, allergic reaction to anaphylaxis may occur.
5) Temporary disorder of systemic and/or local neural network may occur. Sensitivity to stimulus or pain may be abnormal. Vascular, cerebral, or neuronal inflammation (e.g., Guillain-Barre syndrome) resulting in paralysis, neuropathic pain, bleeding, and internal bleeding has been reported.
6) Safety of SKYCellflu Quadrivalent was assessed in a study with 449 children 6 months through 35 months of age, 255 pediatric and adolescent subjects 3 through 18 years of age, and 802 adults ≥ 19 years of age, and

followings were reported for adverse reactions. 701 out of 1,506 (46.55%) subjects developed adverse reactions after vaccination. The incidence rate was 50.11% in children 6 through 35 months of age, 46.27% in pediatric and adolescent subjects 3 through 18 years of age, 49.00% in adult 19 through 59 years of age, and 26.14% in subjects ≥ 60 years of age.

① Solicited adverse reactions observed during the 7-day period after SKYCellflu Quadrivalent vaccination are shown below.

		Total (n = 1,506)	6 through 35 months of age (n = 449)	3 through 18 years of age (n = 255)	19 through 59 years of age (n = 649)	≥ 60 years of age (n = 153)
Local reaction	Tenderness	25.68%	20.27%	37.68%[1]	32.20%	8.50%
	Pain	24.77%		30.59%	29.28%	9.15%
	Erythema/redness	14.54%	27.39%	19.61%	6.47%	2.61%
	Induration/swelling	6.11%	10.69%	11.37%	2.16%	0.65%
Systemic reaction	Myalgia[2]	14.10%	-	11.37%	16.02%	10.46%
	Fatigue/malaise[3]	11.61%	-	7.77%	13.71%	7.84%
	Headache	7.57%	-	5.49%	8.94%	5.23%
	Diarrhea[4]	1.84%	-	0.00%	2.31%	0.65%
	Vomiting[4]	0.57%	-	0.00%	0.62%	0.65%
	Whining/annoyed[5]	12.60%	16.26%	3.76%	-	-
	Somnolence/exhausted[5]	10.39%	12.69%	4.84%	-	-
	Fever	2.39%	7.57%	0.39%	0.15%	0.00%
	Arthralgia[6]	2.15%	-	2.15%	-	-

[1]Reported in subjects ≥ 12 years of age (n=69).
[2]Reported in subjects ≥ 3 years of age (n=1,057).
[3]Reported in subjects ≥ 5 years of age (n=1,008).
[4]Reported in subjects ≥ 12 years of age (n=871).
[5]Reported in subjects < 12 years of age (n=635).
[6] Reported in subjects ≥ 3 and < 12 years of age (n=186).

② Unsolicited adverse reactions observed during the 21-day (adults) or 28-day (children and adolescents) period after SKYCellflu Quadrivalent vaccination were reported in 35 out of 1,506 (2.32%) subjects. Adverse reactions related to respiratory system in 14 subjects (0.93%) was most frequently observed. Adverse reactions observed during the study period are shown below. (Relatively common: 0.1 to <5%, Rare: <0.1%)

Category	Frequency	
	Relatively common	Rare

Respiratory system	Nasopharyngitis, Upper respiratory tract infection, Rhinorrhea	Pharyngitis, Cough, Herpangina
Gastrointestinal disorders	Diarrhea	Dyspepsia, Vomiting, Decreased Appetite
General disorder and administration site condition	Pyrexia	Injection site pruritus/Injection site warmth
Skin and subcutaneous tissue	Rash	Eczema, Viral rash
Musculoskeletal system	Myalgia	
Nervous system		Paresthesia
Sensory organ		Eye discharge

③ 20 out of 1,506 subjects developed 21 serious adverse events (449 subjects with 0.5 mL for 6 to 35 months after birth were followed by 1 month after vaccination) by 6 months after administration of SKYCellflu Quadrivalent vaccine (2 cases of gastroenteritis, 2 cases of pneumonia, 2 cases of mycoplasma pneumonia, 1 case of acute bronchitis, 1 case of acute stomachache, 1 case of acute pharyngitis, 1 case of bacterial pneumonia, 1 case of bronchopneumonia, 1 case of viral induced wheeze, 1 case of acute gastroenteritis, 1 case of diverticulitis, 1 case of wrist fracture, 1 case of tooth abscess, 1 case of benign prostatic hypertrophy, 1 case of deviated nasal septum, 1 case of benign neoplasm of breast, 1 case of cerebral hemorrhage, 1 case of enuresis) and all of which were concluded to be unrelated to SKYCellflu Quadrivalent except 1 case of acute pharyngitis.

7) Post Marketing Experience

① During this 4-year post marketing surveillance (PMS) in South Korea, among 655 subjects on adults aged 19 years and older, adverse events were reported by 6.87% (45/655 subjects, 69 cases) regardless the causal relationship with the vaccine. No serious adverse events or serious adverse drug reactions were reported. In addition, unexpected adverse events and unexpected adverse drug reactions are shown below according to its frequency.

		Unexpected adverse events regardless the causal relationship with the vaccine were reported by 1.68% (11/655 subjects, 16 cases)	Unexpected adverse drug reactions that causal relationship with the vaccine could not be excluded were reported by 0.76% (5/655 subjects, 6 cases)
Relatively common (0.1 to <5%)	*Respiratory, thoracic, and mediastinal disorders*	Cough, Oropharyngeal pain, Respiratory disorder, Rhinitis allergic	Cough, Oropharyngeal pain
	Nervous system disorders	Dizziness	Dizziness
	General disorders and administration site conditions	Influenza like illness	Influenza like illness
	Infections and Infestations	Acute sinusitis, Tonsillitis, Tracheobronchitis	
	Gastrointestinal disorders	Gastritis	
	Injury, poisoning and	Contusion, Skin abrasion,	

	procedural complications	Thermal burn	

② During this 4-year post marketing surveillance (PMS), among 603 subjects on children and adolescents aged 3 to 18 years, adverse events were reported by 18.57% (112/603 subjects, 222 cases) regardless the causal relationship with the vaccine. No serious adverse events or serious adverse drug reactions were reported. In addition, unexpected adverse events and unexpected adverse drug reactions are shown below according to its frequency.

		Unexpected adverse events regardless the causal relationship with the vaccine were reported by 5.47% (33/603 subjects, 44 cases)	Unexpected adverse drug reactions that causal relationship with the vaccine could not be excluded were reported by 0.50% (3/603 subjects, 3 cases)
Uncommon (≥0.1% to <1%)	*General disorders and administration site conditions*	Asthenia	Asthenia
	Infections and Infestations	Conjunctivitis, Bronchiolitis, Croup infectious, Impetigo, Laryngitis	
	Gastrointestinal disorders	Enteritis, Constipation	
	Respiratory, thoracic, and mediastinal disorders	Nasal obstruction, Rhinitis allergic	
	Skin and subcutaneous tissue disorders	Urticaria	
Common (≥1% to <10%)	*Infections and Infestations*	Bronchitis	

③ At the point of re-examination, analysis and assessment were conducted by comparing the adverse events from the post-marketing surveillance of SKYCellflu Quadrivalent with adverse events reported from all of licensed medicines in South Korea (1989-September 30, 2020). The adverse events identified to occur more frequently in SKYCellflu Quadrivalent are as follows.

- General disorders and administration site conditions: Chills, Vaccination site bruising

4.9 Overdose

No information.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

The efficacy of SKYCellflu Quadrivalent is supported by the immunogenicity data from a Phase I/II clinical trial and three Phase III clinical trials. The immunogenicity was assessed based on the seroprotection rate, seroconversion rate, GMR (Geometric Mean Ratio) and GMT (Geometric Mean Titer), in which were calculated using pre-vaccination and post-vaccination of HI (Hemagglutination inhibition) antibody titers. Throughout the Phase III clinical trials, the immunogenicity was evaluated in total of 1,435 subjects who completed the clinical trial without any major protocol violations. Data obtained from 1,435 subjects administered with SKYCellflu Quadrivalent were as follows.

Adults and elderly aged 19 years or older

Immunogenicity was assessed on 1,495 subjects (Test group: 748 subjects, Control group 1: 371 subjects, Control group 2: 376 subjects) included in the per protocol study (PPS), and the pre-determined efficacy criteria for this vaccine were met and the criteria for non-inferiority and superiority were also met.

Evaluation	Efficacy endpoint	Test group	Control group 1	Control group 2
19- 59 years old (Test group: 596 subjects, control group 1: 297 subjects, control group 2: 303 subjects)	SPR[1)] [CI 95%]	A/H1N1: 98.32% [97.29, 99.35] A/H3N2: 99.50% [98.93, 100.00] B/Y: 98.49% [97.51, 99.47] B/V: 99.16% [98.43, 99.89]	A/H1N1: 97.31% [95.47, 99.15] A/H3N2: 99.66% [99.00, 100.00] B/Y: 99.66% [99.00, 100.00] B/V: 95.96% [93.72, 98.20]	A/H1N1: 99.01% [97.90, 100.00] A/H3N2: 100.00% [100.00, 100.00] B/Y: 94.06% [91.40, 96.72] B/V: 97.36% [95.55, 99.16]
	SCR[2)] [CI 95%]	A/H1N1 52.35% [48.34, 56.36] A/H3N2 53.52% [49.52, 57.53] B/Y 43.79% [39.81, 47.78] B/V 54.70% [50.70, 58.69]	A/H1N1: 54.21% [48.54, 59.88] A/H3N2: 48.15% [42.47, 53.83] B/Y: 36.36% [30.89, 41.83] B/V: 38.72% [33.18, 44.26]	A/H1N1: 51.82% [46.19, 57.44] A/H3N2: 46.53% [40.92, 52.15] B/Y: 24.09% [19.28, 28.91] B/V: 50.83% [45.20, 56.45]
	GMR[3)] [CI 95%]	A/H1N1 4.83±4.33 [4.29, 5.43] A/H3N2 3.80±3.28 [3.45, 4.18] B/Y 3.21±2.88 [2.95, 3.50] B/V 4.08±3.01 [3.73, 4.46]	A/H1N1: 5.49±4.27 [4.66, 6.48] A/H3N2: 3.58±3.46 [3.11, 4.13] B/Y: 2.68±2.62 [2.40, 2.99] B/V: 2.75±2.55 [2.47, 3.06]	A/H1N1: 4.68±4.20 [3.98, 5.51] A/H3N2: 3.38±3.39 [2.95, 3.88] B/Y: 2.00±1.95 [1.86, 2.16] B/V: 3.72±2.99 [3.29, 4.21]
60 years of age and older (Test group: 152 subjects, control group1: 74 subjects, control group 2: 73 subjects)	SPR [CI 95%]	A/H1N1 92.76% [88.64, 96.88] A/H3N2 98.68% [96.87, 100.00] B/Y 94.08% [90.33, 97.83] B/V 96.05% [92.96, 99.15]	A/H1N1: 95.95% [91.45, 100.00] A/H3N2: 98.65% [96.02, 100.00] B/Y: 94.59% [89.44, 99.75] B/V: 87.84% [80.39, 95.28]	A/H1N1: 94.52% [89.30, 99.74] A/H3N2: 100.00% [100.00, 100.00] B/Y: 94.52% [89.30, 99.74] B/V: 98.63% [95.96, 100.00]
	SCR [CI 95%]	A/H1N1 52.63% [44.69, 60.57] A/H3N2 42.11% [34.26, 49.95] B/Y 43.42% [35.54, 51.30] B/V 59.87% [52.08, 67.66]	A/H1N1: 45.95% [34.59, 57.30] A/H3N2: 37.84% [26.79, 48.89] B/Y: 37.84% [26.79, 48.89] B/V: 60.81% [49.69, 71.93]	A/H1N1: 43.84% [32.45, 55.22] A/H3N2: 45.21% [33.79, 56.62] B/Y: 27.40% [17.17, 37.63] B/V: 60.27% [49.05, 71.50]

	GMR [CI 95%]	A/H1N1 4.07±3.19 [3.39, 4.90] A/H3N2 3.27±3.39 [2.69, 3.97] B/Y 2.99±2.44 [2.59, 3.44] B/V 4.61±2.79 [3.91, 5.42]	A/H1N1: 4.56±4.11 [3.31, 6.29] A/H3N2: 2.94±3.68 [2.18, 3.95] B/Y: 2.83±2.81 [2.23, 3.58] B/V: 4.69±2.75 [3.73, 5.90]	A/H1N1: 3.89±4.18 [2.80, 5.40] A/H3N2: 2.84±2.65 [2.27, 3.55] B/Y: 2.06±2.08 [1.74, 2.44] B/V: 4.70±3.13 [3.62, 6.11]
Non-inferiority or superiority assessment comparing control drugs	Post-vaccination GMT ratio adjusted by pre-vaccination GMT[4]. (control group GMT/test group GMT) [CI 95%]	A/H1N1: 1.02 [0.94, 1.10] A/H3N2: 0.94 [0.87, 1.01] B/Y: (control group 1) 0.88 [0.82, 0.95], (control group 2) 0.75 [0.70, 0.81] B/V: (control group 1) 0.75 [0.69, 0.81], (control group 2) 0.90 [0.83, 0.97]		
	SCR margin (control group SCR - test group SCR)[CI 95%]	A/H1N1: -1.00 [-6.07, 4.06] A/H3N2: -5.02 [-10.08, 0.04] B/Y: (control group 1) –7.06% [-13.12, -1.00)], (control group 2) -18.98 [-24.61, -13.36] B/V: (control group 1) -12.62 [-18.79, -6.45)], (control group 2) –3.09% [-9.26, 3.09]		

1) SPR (Seroprotection rate): The proportion of subjects with post-vaccination HI titers of ≥ 1:40

2) SCR (Seroconversion rate): The proportion of subjects achieving one of the following conditions;

- If the pre-vaccination HI titer were < 1:10, subjects achieving an HI titer ≥ 1:40 after vaccination

- If the pre-vaccination HI titer were ≥1:10, subjects with a minimum 4-fold rise in HI titer

3) GMR (Geometric mean ratio): Geometric mean fold ratio of mean increase in HI titer at post-vaccination compared to pre-vaccination.

4) GMT (Geometric mean titer): The mean antibody titer for a group of subjects

<u>Children and adolescents aged 3 to 18 years</u>

Immunogenicity was assessed on 314 subjects (Test group: 253 subjects, Control group: 61 subjects) included in the PPS, and the pre-determined efficacy criteria for this vaccine were met.

Evaluation subject	Efficacy endpoints	Test group	Control group
3 to 8 years of age	SPR [CI 95%]	A/H1N1: 100.00% [97.11, 100.00] A/H3N2: 100.00% [97.11, 100.00] B/Y: 90.48% [83.95, 94.98] B/V: 92.86% [86.87, 96.68]	A/H1N1: 100.00% [88.43, 100.00] A/H3N2: 100.00% [88.43, 100.00] B/Y: 90.00% [73.47, 97.89] B/V: 76.67% [57.72, 90.07]
	SCR [CI 95%]	A/H1N1: 53.97% [45.27, 62.67] A/H3N2: 50.00% [41.27, 58.73] B/Y: 68.25% [60.13, 76.38] B/V: 61.90% [53.43, 70.38]	A/H1N1: 50.00% [32.11, 67.89] A/H3N2: 46.67% [28.81, 64.52] B/Y: 56.67% [38.93, 74.40] B/V: 20.00% [5.69, 34.31]
	GMR [CI 95%]	A/H1N1: 3.43±2.50 [2.92, 4.03] A/H3N2: 2.56±2.17 [2.23, 2.94]	A/H1N1: 2.89±2.15 [2.17, 3.85] A/H3N2: 2.58±1.85 [2.05, 3.25]

		B/Y: 4.72±2.31 [4.07, 5.47] B/V: 4.07±2.50 [3.46, 4.78]	B/Y: 4.00±2.16 [3.00, 5.34] B/V: 2.24±2.17 [1.68, 3.00]
9 to 18 years of age	SPR [CI 95%]	A/H1N1: 100.00% [97.14, 100.00] A/H3N2: 100.00% [97.14, 100.00] B/Y: 100.00% [97.14, 100.00] B/V: 95.28% [90.00, 98.25]	A/H1N1 96.77% [83.30, 99.92] A/H3N2 100.00% [88.78, 100.00] B/Y 100.00% [88.78, 100.00] B/V 83.87% [66.27, 94.55]
	SCR [CI 95%]	A/H1N1: 50.39% [41.70, 59.09] A/H3N2: 47.24% [38.56, 55.93] B/Y: 49.61% [40.91, 58.30] B/V: 43.31% [34.69, 51.92]	A/H1N1 67.74% [51.29, 84.20] A/H3N2 58.06% [40.69, 75.44] B/Y 54.84% [37.32, 72.36] B/V 22.58% [7.86, 37.30]
	GMR [CI 95%]	A/H1N1: 2.98±2.50 [2.54, 3.50] A/H3N2: 2.53±2.27 [2.19, 2.92] B/Y: 3.11±2.28 [2.69, 3.60] B/V: 3.01±2.29 [2.60, 3.48]	A/H1N1 5.35±3.18 [3.50, 8.18] A/H3N2 2.86±2.22 [2.13, 3.83] B/Y 3.34±2.58 [2.36, 4.73] B/V 2.00±2.32 [1.47, 2.72]

Children aged 6 months to 35 months of age

Immunogenicity was assessed on 653 subjects (Test group: 434 subjects, Control group: 219 subjects) included in the PPS, and the pre-determined efficacy criteria for this vaccine were met and the criteria for non-inferiority and superiority were also met.

Evaluation subject	Efficacy endpoints	Test group	Control group
6 months to 35 months of age	SPR [CI 95%]	A/H1N1: 95.16% [93.14, 97.18] A/H3N2: 95.85% [93.98, 97.73] B/Y: 59.68% [55.06, 64.29] B/V: 52.53% [47.84, 57.23]	A/H1N1: 93.15% [89.81, 96.50] A/H3N2: 94.52% [91.51, 97.53] B/V: 42.92% [36.37, 49.48]
	SCR [CI 95%]	A/H1N1: 87.56% [84.45, 90.66] A/H3N2: 87.56% [84.45, 90.66] B/Y: 57.83% [53.19, 62.48] B/V: 51.38% [46.68, 56.08]	A/H1N1: 85.84% [81.23, 90.46] A/H3N2: 89.50% [85.44, 93.56] B/V: 42.92% [36.37, 49.48]
	GMR [CI 95%]	A/H1N1: 13.43±3.27 [12.01, 15.02] A/H3N2: 12.00±2.94 [10.84, 13.29] B/Y: 6.11±2.79 [5.54, 6.73] B/V: 4.89±2.82 [4.44, 5.39]	A/H1N1: 12.54±3.05 [10.81, 14.55] A/H3N2: 17.02±3.15 [14.61, 19.83] B/V: 4.57±2.87 [3.97, 5.25]
	Post-vaccination GMT Ratio (control group GMT/test group GMT) [CI 95%]	A/H1N1: 1.09 [0.95, 1.27] A/H3N2: 1.31 [1.13, 1.52] B/V: 0.93 [0.78, 1.10]	
	SCR margin (control group SCR- test group SCR)[CI 95%]	A/H1N1: -1.71 [-7.28, 3.85] A/H3N2: 1.94 [-3.17, 7.05] B/V: -8.46 [-16.53, -0.39]	

In conclusion, the immunogenicity results of four clinical trials suggest that SKYCellflu Quadrivalent has a satisfactory immunogenicity profile for all four strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard based on conventional repeat dose toxicity studies. SKYCellflu Quadrivalent was well tolerated and immunogenic in mice. In a repeat-dose toxicity study in rabbits and mice, there was no evidence of systemic toxicity and the vaccine was locally well tolerated.
No evidence of reproductive or developmental toxicity was seen in a study where the human dose was administered prior to and during gestation to female rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Potassium chloride
Potassium dihydrogen phosphate
Disodium phosphate dihydrate
Magnesium chloride hexahydrate
Calcium chloride dihydrate
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

1 year

6.4 Special precautions for storage

1) Store SKYCellflu Quadrivalent refrigerated at 2°C to 8°C away from light. Do NOT freeze.
2) Do not use the vaccine if the contents have been frozen, because it may cause changes in product quality.

6.5 Nature and contents of container

0.5 mL suspension in pre-filled syringes (type I glass) with a plunger stopper (bromobutyl)
Pack size: One pack containing 10 pre-filled syringes, each with needle.
One pack containing 1 pre-filled syringe with needle.

6.6 Special precautions for disposal and other handling

1) Inspect the vaccine visually for any particulate matter or change in physical appearance prior to administration.

2) Before administering a dose of vaccine, shake the vaccine well until colorless or opalescent solution is achieved. Do not use the vaccine in case of any abnormality are observed.
3) Remove the vaccine from the refrigerator and allow reaching room temperature. Shake well to achieve homogenous solution before use (storage condition is 2°C to 8°C refrigeration).
4) Upon long-term storage, vaccine may show slight aggregation. This does not indicate abnormal quality, and is easily resuspended by shaking the vaccine.
5) Do not administer SKYCellflu Quadrivalent via intravenous injection.
6) Lateral upper arm is the typical administration site, and should be disinfected with ethanol or iodine tincture before the administration. In addition, it is advised to avoid repeating vaccination at the same site.

Any unused medicinal product or other waste material should be disposed of in accordance with local rules for the disposal of products of this nature.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

7.1 Marketing authorization holder in South Korea

SK bioscience Co., Ltd.
310 Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

7.2 Marketing authorization holder in Thailand

Bionovel Co., Ltd.
1993 Moo 4, Soi Sukhumvit 115 (Apichart), Sukhumvit Road, Theparak, Muang Samutprakarn 10270, Thailand. Tel. 02 384 7472 Fax. 02 757 7551

7.3 Manufacturer

SK bioscience Co., Ltd.
150, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, 36618, Republic of Korea

8. MARKETING AUTHORISATION NUMBER(S)

2C 12/66 (NB)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 24 August 2023

10. DATE OF REVISION OF THE TEXT

Date of revision: 21 August 2023