Registration No. 2C 2/62 (NBC)

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

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SKYCellflu Quadrivalent prefilled syringe
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)
(2020-2021 season)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Influenza virus surface antigens (hemagglutinin and neuraminidase)*, inactivated, of the following strains:

[A/Guangdong-Maonan/SWL1536/2019, CNIC-1909 (H1N1)]	15 µg HA**
[A/Hong Kong/2671/2019, NIB-121 (H3N2)]	15 µg HA**
[B/Washington/02/2019]	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 2020-2021 season.

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 3 years of age and older.
The use of SKYCellflu Quadrivalent should be based on official recommendations.

4.2 Posology and method of administration

Posology
1) 3 through 8 years of age: 0.5 mL as a single injection.
2) 9 years 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.

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.

Administer SKYCellflu Quadrivalent with caution to the following individuals.
1) Pregnant women or women of child-bearing potential
2) Patients with chronic cardiovascular or respiratory disease or patients with diabetes mellitus may experience significant exacerbation of existing disease upon influenza infection, and thus may receive vaccination with caution, as necessary.
3) 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. SKYCellflu Quadrivalent should be administered to pregnant women or women of child-bearing potential only if clearly needed.

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 two phase III clinical trials. Three human clinical studies have been performed with SKYCellflu Quadrivalent and the safety was evaluated in the Safety Analysis Set of 1,167 subjects who were enrolled and received the vaccination with SKYCellflu Quadrivalent. Of 1,167 subjects who received the SKYCellflu Quadrivalent, 110 healthy infant subjects received 0.25 mL, while 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 and SAEs have been collected during six months of follow-up. Safety analysis for 110 infant subjects from 6 months to 2 years of age were excluded from this summary of product characteristics.

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 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. 476 out of 1,057 (45.03%) subjects developed adverse reactions after vaccination. The incidence rate was 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 = 1,057)	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[1]	28.59%	37.68%	32.20%	8.50%
	Pain	26.58%	30.59%	29.28%	9.15%
	Erythema/redness	9.08%	19.61%	6.47%	2.61%
	Induration/swelling	4.16%	11.37%	2.16%	0.65%
Systemic reaction	Myalgia	14.10%	11.37%	16.02%	10.46%
	Fatigue/malaise[2]	11.61%	7.77%	13.71%	7.84%
	Headache	7.57%	5.49%	8.94%	5.23%
	Diarrhea	1.51%	-	2.31%	0.65%
	Vomiting	0.47%	-	0.62%	0.65%
	Whining/annoyed[3]	3.76%	3.76%	-	-
	Somnolence/exhausted[3]	4.84%	4.84%	-	-
	Fever	0.19%	0.39%	0.15%	-
	Arthralgia[3]	2.15%	1.57%	-	-

[1]Reported in subjects ≥ 12 years of age (n=871). [2]Reported in subjects ≥ 5 years of age (n=1,008).
[3]Reported in subjects 3 through 11 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 7 out of 1,057

(0.66%) subjects. Adverse reactions related to musculoskeletal system was most frequently observed. Adverse reactions observed during the study period are shown below.
(Uncommon: 0.1 to <5%, Rare: <0.1%)

Category	Frequency	
	Uncommon	Rare
Respiratory system		Nasopharyngitis
Musculoskeletal system	Myalgia	
Nervous system		Paresthesia
Skin and subcutaneous tissue		Eczema
General disorder and administration site condition		Injection site pruritus/Injection site warmth

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 the three 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 HAI (Hemagglutination inhibition) antibody titers. The immunogenicity was evaluated in total of 1,158 subjects who completed the clinical trial without any major protocol violations. Data obtained from 1,158 subjects administered with SKYCellflu Quadrivalent were as follows.

Table 1. Immunogenicity Endpoints of SKYCellflu Quadrivalent in Phase I/II Clinical Trial and Phase III Clinical Trials

		Phase I/II Clinical Trials (n=50)	Phase III Clinical Trials (n=360)	Phase III Clinical Trials (n=596)	Phase III Clinical Trials (n=152)
Age groups		19 through 59 years of age	6 months through 18 years of age	19 through 59 years of age	≥ 60 years of age
A/H1N1	Seroprotection rate (%)	94.00	97.50	98.32	92.76
	Seroconversion rate (%)	84.00	62.78	52.35	52.63
	GMR	12.47	4.54	4.83	4.07
A/H3N2	Seroprotection rate (%)	100.00	98.89	99.50	98.68

	Seroconversion rate (%)	66.00	57.78	53.52	42.11
	GMR	7.26	3.60	3.80	3.27
B/Yamagata	Seroprotection rate (%)	100.00	85.56	98.49	94.08
	Seroconversion rate (%)	70.00	59.44	43.79	43.42
	GMR	4.86	4.36	3.21	2.99
B/Victoria	Seroprotection rate (%)	92.00	81.39	99.16	96.05
	Seroconversion rate (%)	70.00	50.00	54.70	59.87
	GMR	4.92	3.61	4.08	4.61

In phase I/II clinical trial which involved 50 subjects vaccinated with SKYCellflu Quadrivalent, sufficient immunogenicity was elicited by SKYCellflu Quadrivalent as the results met CPMP criteria (Seroprotection rate > 70%, Seroconversion rate > 40%, GMR > 2.5) for all four strains.

In phase III clinical trials, the overall results of subjects aged 6 months to 59 years satisfied CPMP criteria for all four strains. Furthermore, subjects aged 60 years or older also met the criteria (Seroprotection rate > 60%, Seroconversion rate > 30%, GMR > 2.0) for all four strains.

Table 2. Primary Immunogenicity Endpoints of SKYCellflu Quadrivalent in Phase III Clinical Trial in Healthy Adults

	Adjusted GMT			GMT Ratio (95% CI[†])
	TIV-1[a] (n=371)	TIV-2[b] (n=376)	SKYCellflu Quadrivalent[c] (n=748)	Pooled TIV[d]/SKYCellflu Quadrivalent
A/H1N1	334.98		329.76	1.02 (0.94, 1.10)
A/H3N2	377.34		401.21	0.94 (0.87, 1.01)
B/Yamagata	144.65	-	163.74	0.88 (0.82, 0.95)
B/Victoria	-	112.20	124.82	0.90 (0.83, 0.97)
	Seroconversion rate (%)			Difference (95% CI[†])
	TIV-1[a] (n=371)	TIV-2[b] (n=376)	SKYCellflu Quadrivalent[c] (n=748)	Pooled TIV[d] - SKYCellflu Quadrivalent
A/H1N1	51.4		52.41	-1.00 (-6.07, 4.06)
A/H3N2	46.18		51.20	-5.02 (-10.08, 0.04)
B/Yamagata	36.66	-	43.72	-7.06 (-13.12, -1.00)
B/Victoria	-	52.66	55.75	-3.09 (-9.26, 3.09)

[†]CI: Confidential Interval

[a]TIV-1 containing A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2) and B/Massachusetts/2/2012 (Yamagata lineage), 2014-2015

[b]TIV-2 containing A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2) and B/Brisbane/60/2008 (Victoria lineage), 2014-2015

[c]SKYCellflu Quadrivalent containing A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2), B/ Massachusetts/2/2012 (Yamagata lineage), B/Brisbane/60/2008 (Victoria lineage), 2014-2015
[d]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

SKYCellflu Quadrivalent demonstrated its immunological non inferiority to both of comparators as the upper limit of 95% CI for the adjusted GMT ratio of comparator over SKYCellflu Quadrivalent was ≤ 1.5 for all strains and the upper limit of the 95% CI for the difference in seroconversion rate of comparator minus SKYCellflu Quadrivalent did not exceed 10% for all four strains.

In conclusion, the immunogenicity results of three 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 (polyisoprene)
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 Korea

SK Bioscience Co.,Ltd.
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7.2 Marketing authorization holder in Thailand

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7.3 Manufacturer

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8. MARKETING AUTHORISATION NUMBER(S)

2C 2/62 (NBC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

January 18, 2019

10. DATE OF REVISION OF THE TEXT

August 21, 2020