Registration No. 2C 3/62 (NBC)

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

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SKYCellflu prefilled syringe
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)
(2016/2017 season)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

A/Christchurch/16/2010, NIB-74xp(H1N1)	15 µg HA**
A/Hong Kong/4801/2014, NYMC X-263(H3N2)	15 µg HA**
B/Brisbane/60/2008, NYMC BX-35	15 µg HA**
	per 0.5 mL dose
A/Christchurch/16/2010, NIB-74xp(H1N1)	7.5 µg HA**
A/Hong Kong/4801/2014, NYMC X-263(H3N2)	7.5 µg HA**
B/Brisbane/60/2008, NYMC BX-35	7.5 µg HA**
	per 0.25 mL dose

*propagated in Madin Darby Canine Kidney (MDCK) cells
**hemagglutinin
The vaccine complies with the WHO recommendation (northern hemisphere) for the 2016/2017 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.
The use of SKYCellflu should be based on official recommendations.

4.2 Posology and method of administration

Posology

1) 6 through 35 months of age: 0.25 mL as a single injection.

2) 3 years of age and older: 0.5 mL as a single injection.

For children below 9 years of age who have not previously been 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
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) Cardiovascular disease, renal disease, or hepatic disease in acute, exacerbation, or active phase
7) Acute respiratory disease or other active infection
8) History of anaphylaxis reaction to any ingredient in SKYCellflu
9) History of suspected allergic reaction, including systemic rash, to previous vaccination
10) Other medical conditions that are diagnosed to be inappropriate for administration of SKYCellflu 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 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 unless the potential benefit outweighs the risk of administration. If the decision is made to administer SKYCellflu 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 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 in pregnant women and breast-feeding women has not been assessed in clinical trials.

<u>Pregnant women</u>

Direct and/or indirect adverse effect related to reproduction and developmental toxicity was not observed in animal studies. SKYCellflu should be administered to pregnant women or women of child-bearing potential only if clearly needed.

<u>Breast-feeding women</u>

Since it is not known whether SKYCellflu is excreted in breast milk, caution should be exercised when SKYCellflu 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 has been assessed in phase I and III clinical trials performed as part of the development program. Overall 1,396 single doses of SKYCellflu were administered to 885 adults aged 19-59 years of age, to 210 elderly (aged 60 years or older), and 301 pediatric and adolescent subjects aged 6 months through 18 years of age. Safety evaluations were performed for all subjects during the first 3 weeks (adults) or 4 weeks (pediatric and adolescent subjects) following vaccination and SAEs have been collected during six months of follow-up.

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 days to 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 was assessed in a study with 301 pediatric and adolescent subjects 6 months through 18 years of age, and 1,095 adult 19 through 59 years of age and followings were reported for adverse reactions. 724 out of 1,396 (51.86%) subjects developed adverse reactions after vaccination. The incidence was 44.85% in pediatric and adolescent subjects 6 months through 18 years of

age, 59.10% in adult subjects 19 through 59 years of age, and 31.43% in subjects ≥ 60 years of age.

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

		Total (n = 1,396)	6 months through 18 years of age (n = 301)	19 through 59 years of age (n = 885)	≥ 60 years of age (n = 210)
Local reaction	Tenderness	26.36%	7.64%	36.16%	11.90%
	Pain	29.51%	30.56%	32.43%	15.71%
	Erythema/redness	8.31%	15.28%	6.55%	5.71%
	Induration/swelling	3.87%	9.97%	2.37%	1.43%
Systemic reaction	Myalgia	18.48%	9.63%	23.16%	11.43%
	Fatigue/malaise[1]	16.69%	5.32%	21.81%	11.43%
	Headache	10.60%	3.99%	14.24%	4.76%
	Diarrhea	2.22%	-	3.28%	0.95%
	Vomiting	0.43%	-	0.56%	0.48%
	Whining/annoyed	1.36%	6.31%	-	-
	Somnolence/exhausted	1.22%	5.65%	-	-
	Fever	0.50%	2.33%	-	-
	Arthralgia	0.14%	0.66%	-	-

[1]Reported in subjects ≥ 5 years of age.

② Adverse reactions observed during the 21-day (adults) or 28-day (pediatric and adolescent subjects) period after SKYCellflu vaccination were reported in 42 out of 1,396 (3.01%) subjects. Adverse reactions related to nervous system and skin and subcutaneous tissue were the most frequently observed, as 10 subjects (0.72%) were reported at each category. 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, cough, wet cough, oropharyngeal pain	Rhinitis, nasal congestion, sneeze, peritonsillar abscess[1], rhinorrhea, sinusitis

Skin and subcutaneous tissue	Pruritus, urticaria	Rash[2]
Nervous system	Headache, dizziness	
Gastrointestinal system	Dyspepsia, nausea	Salivary gland pain
Hepatobiliary system		Hepatic dysfunction
Blood and lymphatic system		Eosinophilia
General disorder and administration site condition	Injection site pruritus	Fatigue, pain, burning sensation, edema

[1]Reported in subjects ≥ 9 years and ≤ 18 years of age. [2]Reported in subjects ≥ 6 months and < 3 years of age.

4.9 Overdose
No information.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB02

The efficacy of SKYCellflu is supported by the immunogenicity data from the three clinical trials. The immunogenicity was assessed based on the seroprotection rate, seroconversion rate and GMR (Geometric Mean Ratio), in which were calculated using pre-vaccination and post-vaccination of HAI (Hemagglutination inhibition) antibody titers. The immunogenicity was evaluated in total 1,373 subjects who completed a clinical trial without any major protocol violations. Data obtained from all subjects administered with SKYCellflu were as follows.

		Phase I Clinical Trial	Phase III Clinical Trial		Phase III Clinical Trial
Age groups (Number of subjects)		20 through 59 years of age (n=50)	19 through 59 years of age (n=818)	60 years old or older (n=208)	6 months through 18 years of age (n=297)
A/H1N1	Seroprotection rate (%)	96.00	98.53	97.12	97.64

	Seroconversion rate (%)	64.00	67.48	64.90	80.81
	GMR	7.16	7.99	6.84	9.29
A/H3N2	Seroprotection rate (%)	100.00	98.53	99.04	98.99
	Seroconversion rate (%)	30.00	52.44	43.27	47.81
	GMR	2.46	4.23	3.09	3.09
B	Seroprotection rate (%)	92.00	96.94	87.50	83.16
	Seroconversion rate (%)	56.00	51.10	40.87	48.15
	GMR	4.79	3.65	2.81	3.14

In phase I clinical trial which involved 50 subjects vaccinated with SKYCellflu, sufficient immunogenicity elicited by SKYCellflu was confirmed, with exception to seroconversion rate and GMR of A/H3N2 strain as they did not meet the CPMP criteria (Seroprotection rate > 60%, Seroconversion rate > 30%, GMR > 2.0).
However, in following two phase III clinical trials, 1,026 adult subjects and 297 pediatric subjects vaccinated with SKYCellflu and their overall seroprotection rate, seroconversion rate and GMR for all three strains met the CPMP criteria.

In conclusion, the results of all three clinical trials demonstrated that SKYCellflu was highly immunogenic in all subjects, as the seroprotection rate, seroconversion rate and GMR for all strains exceeded the CPMP criteria. There was no inconsistent trend of immunogenicity profile of SKYCellflu between the studies.

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 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 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 plunger stopper (polyisoprene)

Pack size: one pack containing 1 or 10 pre-filled syringes, each with needle.

0.25 mL suspension in pre-filled syringes (type I glass) with plunger stopper (polyisoprene)

Pack size: one pack containing 1 or 10 pre-filled syringes, each 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 via intravenous injection.
6) Lateral upper arm is the typical administration site of children 1 year of age and above or adult. The anterolateral thigh is the administration site of children less

than 1 year of age. The injection site 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 3/62 (NBC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

January 18, 2019

10. DATE OF REVISION OF THE TEXT

February 18, 2019