Registration No. 2C 2/63 (NBC)
Importer / Manufacturer: Bionovel Co.,Ltd./ SK Bioscience Co., Ltd.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

SKYCellflu inj

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Description

SKYCellflu inj., an inactivated influenza virus vaccine, for intramuscular use, is prepared from influenza viruses propagated in MDCK-Sky3851 cells. For virus inactivation, formaldehyde is used, and removed by purification process. There is no thimerosal used in the manufacturing process of 0.5 mL single-dose presentation of SKYCellflu inj. Antibiotics are not used in the manufacture of SKYCellflu inj. SKYCellflu inj. may contain residual amounts of formaldehyde (not more than 10 μg/dose) and polysorbate 80 (not more than 50 μg/dose)

Each 0.5 mL vial contains

Purified inactivated influenza virus surface antigen [A/Michigan/45/2015, NYMC X-275 (H1N1)] (In-house)	15 μg
Purified inactivated influenza virus surface antigen [A/Singapore/INFIMH-16-0019/2016, IVR-186 (H3N2)] (In-house)	15 μg
Purified inactivated influenza virus surface antigen [B/Maryland/15/2016] (In-house)	15 μg

Season 2018/2019

3. PHARMACEUTICAL FORM

Clear or slightly opalescent liquid contained within colorless and transparent vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunization for the prevention of influenza caused by influenza type A viruses and type B virus in children, adolescents and adults aged 6 months and older.

4.2 Posology and method of administration

[Dosage and schedule]

Following dose is administered via intramuscular injection, and same dose is repeated once annually.

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 been previously vaccinated or infected, a second dose should be administered after an interval of at least 4 weeks.

[Instruction for administration]

In case of administration to children aged 6 to 35 months by taking 0.25 mL of this vaccine, the vial containing the remainder should be IMMEDIATELY discarded.

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 2~8°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 inj. 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.

4.3 Contraindication

N/A

4.4 Special warnings and precautions for use

1. General precautions

1) Clean the injection site before vaccine administration. Immediately seek medical attention if symptoms such as convulsion develop after vaccination.
2) Antibody response may be insufficient in patients with inherited or iatrogenic immunodeficiency.
3) Influenza vaccine should be administered before influenza outbreaks. Vaccination may be delayed depending on epidemiological situation.
4) Influenza vaccine should be administered annually using new vaccine composed with strains recommended each year.
5) SKYCellflu inj. can prevent disease caused by influenza virus only, and does not prevent infection caused by other sources which show similar symptoms as influenza.
6) As with other injectable vaccine preparations, appropriate emergency intervention should be prepared for potential anaphylaxis response after administration of the vaccine.
7) Syncope may occur after or even before vaccination as a psychological reaction to injection needle. Appropriate measures should be taken to prevent injury from syncope.

[Precautions for use]

2. Do not administer SKYCellflu inj. to the following individuals.

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 formaldehyde) in SKYCellflu inj.

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 inj.

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 inj.

3. Administer SKYCellflu inj. with caution to the following individuals.

1)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.

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

4.5 Interaction with other medical products and forms of interaction

1. Concurrent immunosuppressive therapy or immunodeficiency may affect immunological response to the vaccine.
2. Co-administration of SKYCellflu inj. 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 Pregnancy and lactation

1. Safety of SKYCellflu inj. has not been evaluated in pregnant women. Direct and/or indirect adverse effect related to reproduction and developmental toxicity was not observed in animal studies. SKYCellflu inj. should be administered to pregnant women or women of child-bearing potential only if clearly needed.
2. Safety of SKYCellflu inj. has not been evaluated in breastfeeding women. Since it is not known whether SKYCellflu inj. is excreted in breast milk, caution should be exercised when SKYCellflu inj. is administered to a nursing mother.

4.7 Effects on the ability to drive and use machines

N/A

4.8 Undesirable effects

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 aged 19 years and older, 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 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 (children and adolescent) 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		Eosinophilia

system		
General disorder and administration site condition	Injection site pruritus	Fatigue, pain, feeling hot, oedema

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

③ 13 out of 1,396 subjects developed 17 serious adverse events by 21 days or 28 days after SKYCellflu vaccination (4 events of gastroenteritis, 2 events of acute cholecystitis, 2 events of asthma, 1 event of bronchitis, 1 event of hand-foot-mouth disease, 1 event of nasopharyngitis, 1 event of tonsilitis, 1 event of inguinal hernia, 1 event of left knee injury, 1 event of right gastrocnemius muscle rupture, 1 event of acute appendicitis, 1 event of lymphadenitis), all of which were concluded to be unrelated to SKYCellflu. 41 out of 1,396 subjects developed 51 serious adverse events by 6 months after SKYCellflu vaccination (6 events of gastroenteritis, 3 events of influenza, 3 events of bronchitis, 3 events of pneumonia, 2 events of herniated intervertebral disc, 2 events of acute cholecystitis, 2 events of pharyngotonsillitis, 2 events of asthma, 1 event of oral abscess, 1 event of appendicitis, 1 event of nasal septal deviation, 1 event of cervical stenosis, 1 event of intracranial aneurysm, 1 event of hemorrhoid, 1 event of cervical dysplasia, 1 event of endometrial polyp, 1 event of hydronephrosis, 1 event of contusion, 1 event of diffuse axonal injury, 1 event of muscle rupture, 1 event of traffic accident, 1 event of chronic hepatitis, 1 event of lymphadenitis, 1 event of postural vertigo, 1 event of uterine leiomyoma, 1 event of intervertebral disorder, 1 event of cellulitis, 1 event of hand-foot-mouth disease, 1 event of nasopharyngitis, 1 event of pharyngitis, 1 event of tonsillitis, 1 event of tonsil hypertrophy, 1 event of myocarditis, 1 event of inguinal hernia, 1 event of wound, and 1 event of epilepsy), all of which were concluded to be unrelated to SKYCellflu.

4.9 Overdose

No information.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not applicable

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Magnesium chloride hexahydrate, Calcium chloride dihydrate, Sodium chloride, Potassium chloride, Potassium dihydrogen phosphate, Disodium phosphate dihydrate.

Solvent: Water for injection (EP)

6.2 Incompatibilities

N/A

6.3 Shelf life

1 year

6.4 Special precautions for storage

1) Store SKYCellflu inj. refrigerated at 2~8°C away from light.
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/vial x10

Pack size: 10 vials in a cardboard box.

6.6 Special precautions for disposal and other handling

N/A

7. MARKETING AUTHORISATION HOLDER

Bionovel Co., Ltd.

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8. MARKETING AUTHORISATION NUMBER(S)

2C 2/63 (NBC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

July 8, 2020

10. DATE OF REVISION OF THE TEXT

April 10, 2019