SK bioscience

SKYCellflu Quadrivalent®

prefilled syringe

Influenza vaccine, surface antigen, inactivated, prepared in cell cultures

Intramuscular Inj.

【Composition】 Each 0.5mL prefilled syringe contains:

Active ingredients:

Purified inactivated influenza virus surface antigen [A/Guangdong-Maonan/SWL1536/2019, CNIC-1909 (H1N1)] (In-house) ··· 15μg
Purified inactivated influenza virus surface antigen [A/Hong Kong/2671/2019, NIB-121 (H3N2)] (In-house) ··· 15μg
Purified inactivated influenza virus surface antigen [B/Washington/02/2019] (In-house) ··· 15μg
Purified inactivated influenza virus surface antigen [B/Phuket/3073/2013] (In-house) ··· 15μg

Stabilizers:

Magnesium chloride hexahydrate (EP) ··· 0.050mg
Calcium chloride dihydrate (EP) ··· 0.067mg

Excipients: Sodium chloride, Potassium chloride, Potassium dihydrogen phosphate, Disodium phosphate dihydrate
Solvent: Water for injection (EP) ··· q.s.
Supplement: Disposable needle (25G×5/8(0.5×16mm)) (In-house) ··· 1 ea
【Appearance】 Clear or slightly opalescent liquid contained within colorless and transparent prefilled syringe.
【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.

【Dosage and administration】

Following dose is administered via intramuscular injection, and same dose is repeated once annually.
1) 3 through 8 years of age: 0.5mL as a single injection.
2) 9 years of age and older: 0.5mL 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.

【Clinical Pharmacology】

1. Mechanism of Action

SKYCellflu Quadrivalent® provides active immunization against the four influenza virus strains (two type A and two type B) contained in the vaccine. Immunity to the surface antigens, particularly the hemagglutinin, reduces the likelihood of infection. Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza virus infection but the HI antibody titers have been used as a measure of vaccine activity. In some human studies, HI antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.
Annual vaccination with the current vaccine is recommended because immunity during the year after vaccination declines, and because circulating strains of influenza virus change from year to year. Protection is conferred only against those strains of virus from which SKYCellflu Quadrivalent® is prepared or closely related strains.

2. Pharmacodynamics

Seroprotection is generally obtained within 3 weeks. The duration of postvaccinal immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually 6-12 months.

2.1 Immunogenicity of SKYCellflu Quadrivalent in adults and elderly subjects

Immunogenicity of SKYCellflu Quadrivalent was assessed by hemagglutinin inhibition (HI) assay in a total of 1,495 subjects, including 1,196 adults from 19 through 59 years of age and 299 subjects from the elderly over 60 years of age. The subjects were randomized in a ratio of 2:1:1 to SKYCellflu Quadrivalent with A/H1N1, A/H3N2, B/Yamagata, B/Victoria strains, NBP607-Y with A/H1N1, A/H3N2, B/Yamagata strains, or NBP607-V with A/H1N1, A/H3N2, B/Victoria strains, and were vaccinated with one dose of the investigational product.
The primary endpoint was to assess non-inferiority of SKYCellflu Quadrivalent in terms of post-vaccination Geometric Mean Titer (post-GMT) and seroconversion rate for all 4 strains in the overall subjects, by determining whether the upper limit of 95% confidence interval for the adjusted post-GMT ratio (comparator/test product) and seroconversion rate difference (comparator-test product) do not exceed 1.5 (≤1.5) and 10% (≤10%), respectively. In addition, it was assessed whether the CHMP criteria were satisfied for each age strata (seroprotection rate ≥70%, seroconversion rate ≥40%, Geometric Mean Ratio (GMR) ≥2.5 for subjects aged from 19 through 59 years; seroprotection rate ≥60%, seroconversion rate ≥30%, GMR ≥2.0 for subjects aged over 60 years).
The results from the age group of adults 19 to 60 years of age and the elderly group of over 60 years of age all met the non-inferiority criteria (see Table 1), and each age strata satisfied the respective CHMP acceptance criteria for all 4 strains. (see Table 2).

Table 1. GMT and seroconversion rate of SKYCellflu Quadrivalent in adults and elderly (PPS*)

		19 to <60 years of age			≥60 years of age		
		NBP607-QIV (N=596)	NBP607-Y (N=297)	NBP607-V (N=303)	NBP607-QIV (N=152)	NBP607-Y (N=74)	NBP607-V (N=73)
A/H1N1	Pre-GMT[1]	80.84	72.02		56.31	61.43	
	Adjust Post-GMT	356.41	369.68		247.99	227.87	
	GMTR[2], Y+V/QIV(95% CI)	1.04(0.95, 1.13)			0.92(0.78, 1.08)		
	SCR[3], N(%)	312(52.35)	318(53.00)		80(52.63)	66(44.90)	
	Diff. Y+V-QIV(95% CI)	0.65(-5.01, 6.31)			-7.73(-19.03, 3.56)		
A/H3N2	Pre-GMT	110.41	118.35		117.34	133.12	
	Adjust Post-GMT	408.03	379.59		380.34	374.21	
	GMTR, Y+V/QIV(95% CI)	0.93(0.86, 1.01)			0.98(0.84, 1.15)		
	SCR, N(%)	319(53.52)	284(47.33)		64(42.11)	61(41.50)	
	Diff. Y+V-QIV(95% CI)	-6.19(-11.85, -0.53)			-0.61(-11.79, 10.57)		
B/Yamagata	Pre-GMT	59.47	65.00	63.21	39.82	37.11	40.38
	Adjust Post-GMT	178.81	156.77	135.58	113.40	102.39	81.83
	GMTR, Y/QIV(95% CI)	0.88(0.81, 0.95)			0.90(0.77, 1.07)		
	SCR, N (%)	261(43.79)	108(36.36)	73(24.09)	66(43.42)	28(37.84)	20(27.40)
	Diff. Y-QIV (95%CI)	-7.43(-14.20, -0.66)			-5.58(-19.15, 7.99)		
B/Victoria	Pre-GMT	33.75	32.88	33.01	21.12	17.38	19.44
	Adjust Post-GMT	133.44	94.48	119.38	94.10	90.82	86.13
	GMTR, V/QIV (95% CI)	0.89(0.82, 0.98)			0.92(0.77, 1.09)		
	GMTR, Y/QIV (95% CI)	0.71(0.65, 0.77)			0.97(0.81, 1.15)		
	SCR, N (%)	326(54.70)	115(38.72)	154(50.83)	91(59.87)	45(60.81)	44(60.27)
	Diff. V-QIV (95% CI)	-3.87(-10.78, 3.03)			0.41(-13.26, 14.07)		
	Diff. Y-QIV (95% CI)	-15.98(-22.81, -9.15)			0.94(-12.64, 14.52)		

* PPS: Per Protocol Set
1) GMT: Geometric Mean Titer, 2) GMTR: Geometric Mean Titer Ratio, 3) SCR: Seroconversion Rate

Table 2. Seroprotection rate, seroconversion rate, GMR of SKYCellflu Quadrivalent in adults and elderly (PPS*)

		19 to <60 years of age (N=596)	≥60 years of age (N=152)
A/H1N1	Seroprotection rate, N(%)	586(98.32)	141(92.76)
	Seroconversion rate, N(%)	312(52.35)	80(52.63)
	GMR[1]	4.83±4.33	4.07±3.19
A/H3N2	Seroprotection rate, N(%)	593(99.50)	150(98.68)
	Seroconversion rate, N(%)	319(53.52)	64(42.11)
	GMR	3.80±3.28	3.27±3.39
B/Yamagata	Seroprotection rate, N(%)	587(98.49)	143(94.08)
	Seroconversion rate, N(%)	261(43.79)	66(43.42)
	GMR	3.21±2.88	2.99±2.44
B/Victoria	Seroprotection rate, N(%)	591(99.16)	146(96.05)
	Seroconversion rate, N(%)	326(54.70)	91(59.87)
	GMR	4.08±3.01	4.61±2.79

* PPS: Per Protocol Set
1) GMR: Geometric Mean Ratio

2.2 Immunogenicity of SKYCellflu Quadrivalent in children and adolescents aged 6 months through 18 years of age

In the paediatric clinical study, the number of subjects for immunogenicity analysis aged 3 through 18 years was 253, including 126 children from a group of 3 through 8 years of age and 127 children from a group of 9 through 18 years of age. Subjects aged 3 through 8 years with no history of influenza infection or influenza vaccination were injected twice with the interval of approximately 4 weeks, while the other subjects were injected once with SKYCellflu Quadrivalent.
Immunogenicity was analyzed by HI assay, and the primary endpoint was to assess seroprotection rate, seroconversion rate, and GMR to determine whether the CHMP criteria were satisfied (seroprotection ≥70%, seroconversion ≥40%, GMR ≥2.5).
The seroprotection rate, seroconversion rate, and GMR for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains all satisfied the CHMP criteria in both age strata (see Table 3).

Table 3. Seroprotection rate, seroconversion rate, GMR of SKYCellflu Quadrivalent in children and adolescents (PPS*)

		3 to <9 years of age (N=126)	9 to <19 years of age (N=127)
A/H1N1	Seroprotection rate(%)	126(100.00)	127(100.00)
	Seroconversion rate(%)	68(53.97)	64(50.39)
	GMR[1](Post/Pre)	3.43±2.50	2.98±2.50
A/H3N2	Seroprotection rate(%)	126(100.00)	127(100.00)
	Seroconversion rate(%)	63(50.00)	60(47.24)
	GMR(Post/Pre)	2.56±2.17	2.53±2.27
B/Yamagata	Seroprotection rate(%)	114(90.48)	127(100.00)
	Seroconversion rate(%)	86(68.25)	63(49.61)
	GMR(Post/Pre)	4.72±2.31	3.11±2.28
B/Victoria	Seroprotection rate(%)	117(92.86)	121(95.28)
	Seroconversion rate(%)	78(61.90)	55(43.31)
	GMR(Post/Pre)	4.07±2.50	3.01±2.29

* PPS: Per Protocol Set
1) GMR: Geometric Mean Ratio

【Precautions for use】

1. Do not administer SKYCellflu Quadrivalent® 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 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) 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 Quadrivalent®
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 Quadrivalent® vaccine.

2. 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 any bleeding disorder, such as hemophilia or thrombocytopenia, or patients on anticoagulant therapy should not receive SKYCellflu Quadrivalent® unless the potential benefits outweigh 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.

3. 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	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

③ 12 out of 1,057 subjects developed 13 serious adverse events by 6 months after administration of SKYCellflu Quadrivalent® vaccine (2 cases of gastroenteritis, 1 cases of diverticulitis, 1 case of wrist fracture, 1 case of tooth abscess, 1 case of benign prostate hyperplasia, 1 case of deviated nasal septum, 1 case of benign neoplasm of breast, 1 case of cerebral hemorrhage, 1 case of acute stomachache, 1 case of pneumonia, 1 case of mycoplasma pneumonia, 1 case of enuresis) and all of which were concluded to be unrelated to SKYCellflu Quadrivalent.®

7) Post Marketing Experience

① During this 4-year post marketing surveillance (PMS), 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)
Uncommon (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 procedural complications	Contusion, Skin abrasion, Thermal burn	

② At the point of re-examination, integrated assessment of adverse events in SKYCellflu was conducted from re-examination reports to MFDS and adverse events from spontaneous reports compared with all reported events in all licensed vaccines in Korea (1989-March 31, 2020). Among the statistically significant adverse events reported on this vaccine compared to those reported on all other vaccines the following are newly identified. However, this does not mean that the causal relationship between the component of this vaccine and the following adverse events has been proved.

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

4. General precautions

1) Instruction should be provided to the vaccine recipient or caregiver to have a rest on the day of vaccination and next day, to maintain the injection site clean, and to immediately seek medical attention if symptoms such as fever and 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 a new vaccine composed with strains recommended each year.
5) SKYCellflu Quadrivalent® 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.

5. Interaction

1) Concurrent immunosuppressive therapy or immunodeficiency may affect immunological response to the vaccine.
2) Co-administration of SKYCellflu Quadrivalent® with other vaccines 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 the 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.

6. Use in pregnant women and nursing mothers

1) Safety of SKYCellflu Quadrivalent® 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 Quadrivalent® should be administered to pregnant women or women of child-bearing potential only if clearly needed.
2) Safety of SKYCellflu Quadrivalent® has not been evaluated in breastfeeding 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.

7. Instruction for administration

1) Remove the vaccine from the refrigerator and allow reaching room temperature before use.
2) Inspect the vaccine visually for any particulate matter or change in physical appearance prior to administration.
3) Upon long-term storage, vaccine may show slight aggregation. This does not indicate abnormal quality, and is easily resuspended by shaking the vaccine.
4) Before administering a dose of vaccine, shake the vaccine well until colorless or opalescent homogenous solution is achieved. Do not use the vaccine in case any abnormalities are observed.
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.

8. Incompatibilities

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

9. Precautions for storage and handling

1) Store SKYCellflu Quadrivalent® refrigerated at 2~8°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.

10. Others

Unit and name of the virus strains recommended annually and used for this vaccine production are specified in【Composition】of this package insert.

【Storage】 Keep refrigerated at 2~ 8°C in a hermetic container away from light. Do NOT freeze.

【Expiration date】 As marked separately on the primary container.

【Packaging units】 0.5mL/prefilled syringe. Supplied in pack size of 1, 5 or 10. *Not all pack sizes may be marketed.*

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(Ver.005)

Manufacturer
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