SKYVaricella Inj.

Varicella Virus Vaccine (live) [Oka/SK]

Prescription drug **Subcutaneous Inj.**

1. Composition

Each 0.5 mL of reconstituted vaccine contains

- **Active ingredients:**
  - Live, attenuated varicella-zoster virus (In-house) ..... ≥ 2,400 PFU
    (Virus strain: Oka/SK, Cell line: MRC-5)
- **Excipients (Stabilizers):**
  - Sucrose (Ph. Eur.) ..... 25.00 mg
  - Hydrolyzed gelatin (NF) ..... 12.50 mg
  - Urea (Ph. Eur.) ..... 1.20 mg
  - Monosodium glutamate (NF) ..... 0.55 mg
  - Disodium edetate (Ph. Eur.) ..... 0.25 mg
  - L-cysteine (JP) ..... 0.25 mg
  - Glycine (Ph. Eur.) ..... 2.50 mg
- **Other Excipients:**
  Sodium dihydrogen phosphate dihydrate, Disodium phosphate dodecahydrate, Sodium chloride, Potassium chloride, Sodium hydroxide
- **Each diluent contains:**
  - Water for injections (Ph. Eur.) ..... 0.7 mL

2. Appearance

Lyophilized white crystalline pellet in a clear colorless vial.
Colorless or pale yellow liquid in the vial when reconstituted to a suspension.

3. Indications

Prevention of varicella in children 12 months to 12 years of age.

4. Dosage and Administration

Total volume (approximately 0.5 mL) of reconstituted vaccine is administered subcutaneously. The outer aspect of the upper arm (deltoid region) is preferred for the site of injection.
If second dose should be administered as per Thai authority recommendation, the following regimen may be applied for children 12 months to 12 years of age.
First dose may be administered at 12-18 months of age. The second dose may be administered at 4-6 years of age. In case of Varicella outbreak, the second dose may be administered before 4 years of age but may be apart from the first dose 3 months at least.

5. Reconstitution and Administration Instructions

To reconstitute the vaccine, withdraw the total volume of provided diluent and inject all withdrawn diluent into the vial of lyophilized vaccine. Gently agitate to dissolve completely. Withdraw the entire contents into the syringe and inject the total volume (approximately 0.5 mL) of reconstituted vaccine subcutaneously into the outer aspect of the upper arm (deltoid region). In order to minimize loss of potency, the vaccine should be administered immediately after reconstitution. Discard the reconstituted vaccine, if not used within 30 minutes.

6. Precautions for Use

6.1 Contraindications

1) Individuals with a history of hypersensitivity reaction to gelatin or any other component in SKYVaricella Inj.
2) Individuals with a history of anaphylactic/anaphylactoid reaction to neomycin (trace amount of neomycin is present in the reconstituted vaccine).

3) Individuals with primary and acquired immunodeficiency states due to conditions such as acute and chronic leukemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS; and cellular immune deficiencies.
4) Individuals on immunosuppressive therapy (SKYVaricella Inj. may cause more severe vaccine-associated rash or disseminated diseases in individuals with immunodeficiency or on immunosuppressive therapy, as the vaccine is live, attenuated varicella virus vaccine).
5) Individuals with active untreated tuberculosis.
6) Pregnant women or women of child-bearing potential (refer to *6.5 Use in Pregnancy and Lactation*).
7) Individuals with febrile respiratory disease or other febrile infections.

6.2 Adverse Reactions

1) Safety of SKYVaricella Inj. was evaluated in 365 subjects aged 12 months to 12 years and 167 subjects (45.75%) experienced adverse drug reactions.
2) Local reaction: Injection site pain/tenderness, erythema/redness, and induration/swelling may occur.
3) Systemic reaction: Fever, whining/irritability, somnolence/exhausted and occasionally systemic reaction such as fatigue/malaise and headache may occur after vaccination.

① Solicited adverse drug reactions† (local and systemic reactions) after vaccination of SKYVaricella Inj. are summarized in below table.

		Phase II clinical trial N=114	Phase III clinical trial N=251
Local reaction	Pain/tenderness	14.04%	20.32%
	Erythema/redness	17.54%	32.67%
	Induration/swelling	6.14%	15.54%
Systemic reaction	Fever	7.02%	7.97%
	Somnolence/exhausted	5.26%	7.57%
	Headache	1.75%	2.39%
	Whining/irritability	11.40%	11.95%
	Fatigue/malaise††	0.00%	12.90%

†Adverse drug reactions were reported as per the planned data collection system and collected for 7 days post-vaccination (N=365).

††Fatigue/malaise was investigated for children aged 5 years and older (Phase II clinical trial N=0/9, Phase III clinical trial N=4/31).

② Unsolicited adverse drug reactions were reported in 16 (4.38%) out of 365 subjects aged 12 months to 12 years during 42 days post-vaccination of SKYVaricella Inj. The most frequently reported unsolicited adverse drug reaction was skin and subcutaneous tissue disorders with 7 subjects (1.92%) reporting 8 cases and followed by infections and infestations with 6 subjects (1.64%) reporting 6 cases. With regard to the outcomes of adverse drug reactions, all subjects were recovered without sequelae. Adverse drug reactions occasionally observed (≥0.1 and <5%) are shown below.

- Gastrointestinal disorders: Vomiting, diarrhea
- Infections and Infestations: Gastroenteritis, nasopharyngitis, upper respiratory tract infection
- General disorders and administration site conditions: Vaccination site erythema
- Metabolism and nutrition disorder: Decreased appetite
- Skin and subcutaneous tissue disorders: Erythema, rash, rash vesicular

③ 7 serious adverse events occurred within 26 weeks post-vaccination in 6 subjects (1.64%) out of 365 subjects (2 cases of bronchiolitis, 1 case of otitis media acute, 1 case of pneumonia, 1 case of upper respiratory tract infection, 1 case of pneumonia respiratory syncytial viral, and 1 case of thermal burn). All of these serious adverse events were confirmed to be not related to SKYVaricella Inj., which were reported in phase III clinical trial.

④ Varicella-like rashes were reported in 6 subjects (1.64%) out of 365 subjects with 6 cases within 42 days post-vaccination, which were reported in phase III clinical trial. Among the cases of varicella-like rash

occurred within 42 days post-vaccination in the phase III clinical trial, 5 cases in 5 subjects were generalized varicella-like rashes and 1 case in 1 subject was injection-site varicella-like rash. In regard to 4 cases of generalized varicella-like rash and 1 case of injection-site varicella-like rash, samples from the lesion of subjects were collected and polymerase chain reaction (PCR) assay was conducted. As a result, varicella-zoster virus was identified in 5 cases, but the virus type (wild type or Oka/SK strain) could not be specified. 2 cases of generalized varicella-like rashes were confirmed to be not related to SKYVaricella Inj. and it was determined that a causal relationship between 3 cases of generalized varicella-like rashes and 1 case of injection-site varicella-like rash and SKYVaricella Inj. could not be ruled out.

6.3 General Precautions

1) As with other vaccines, vaccination with SKYVaricella Inj. does not result in protection of all vaccine recipients.
2) As with other vaccines, anaphylactic/anaphylactoid reaction might occur with SKYVaricella Inj. Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use.
3) Deferral of vaccination should be considered in acute illness (e.g., fever >38.0°C).
4) After blood or plasma transfusion, or administration of immune globulin or varicella-zoster immune globulin, SKYVaricella Inj. should be vaccinated with the minimum interval (3 to 11 months), depending on the type and dose of blood or immunoglobulin.
5) SKYVaricella Inj. should not be given concomitantly with immune globulin including varicella-zoster immune globulin. Also, any immune globulin including varicella-zoster immune globulin should not be given for 2 months thereafter unless its use outweighs the benefit of vaccination.
6) Since Reye syndrome has been reported after the use of salicylates in the case of wild-type varicella infection, the vaccine recipients avoid the use of salicylates for 6 weeks post-vaccination.
7) Transmission of the vaccine virus has not been reported from SKYVaricella Inj. clinical studies. However, it has been confirmed at post-marketing of other varicella virus vaccine that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts and transmission of vaccine virus from vaccinees who do not develop a varicella-like rash has also been reported. Therefore, vaccine recipients should attempt to avoid, whenever possible, close association with susceptible high-risk individuals for up to 6 weeks. In circumstances where contact with high-risk individuals is unavoidable, the potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus. Susceptible high-risk individuals are as follows.
   - Immunocompromised individuals
   - Pregnant women without documented history of chickenpox or laboratory evidence of prior infection
   - Newborn infants of mothers without documented history of chickenpox or laboratory evidence or prior infection

6.4 Interactions

Refer to *6.3 General Precautions for immune globulin, salicylates and transfusion.*

6.5 Use in Pregnancy and Lactation

1) Safety of SKYVaricella Inj. has not been evaluated in pregnant women. Direct and/or indirect adverse effect related to reproductive and developmental toxicity has not been observed in animal studies. However, SKYVaricella Inj. should not be administered to pregnant women since wild-type varicella (natural infection) is known to sometimes cause fetal harm. Furthermore, pregnancy should be avoided for 3 months following vaccination (refer to *6.1 Contraindications*).
2) It is not known whether live attenuated varicella virus is excreted in human milk. However, because some viruses are excreted in human milk, caution should be exercised if SKYVaricella Inj. is administered to nursing mothers.

6.6 Pediatric Use

Since the safety and efficacy of the vaccine for infants less than 12 months of age has not been established, SKYVaricella Inj. is not administered to infants less than 12 months of age.

6.7 Geriatric Use

SKYVaricella Inj. is not used in adults including elderly for the prevention of varicella.

6.8 Precautions for Administration

1) SKYVaricella Inj. should be stored in the refrigerator and reconstituted immediately upon removal from the refrigerator. The vaccine should be used immediately within 30 minutes after reconstitution. Do not freeze reconstituted vaccine.
2) A separate sterile syringe and needle should be used for each injection to prevent transmission of infectious diseases. The used needles should be discarded appropriately to prevent reuse.

6.9 Precautions for Storage and Handling

1) It should be stored in the original package to eliminate the cause of accidents or maintain the quality.
2) It must not be mixed with other medicinal products in one syringe.

6.10 Information for Professionals

1) Pharmacological information
   SKYVaricella Inj. is a live attenuated varicella-zoster virus vaccine (Oka/SK strain) inducing an immune response to varicella infection.
2) Clinical trial information
   Efficacy (Immunogenicity) of SKYVaricella Inj. was assessed with a multi-national, randomized, double-blind, active controlled, parallel clinical trial in healthy children 12 months to 12 years of age. The primary immunogenicity analysis was performed for 458 subjects in per protocol set (PPS) and non-inferiority in seroconversion rate was proven by fluorescent antibody to membrane antigen (FAMA) assay. FAMA assay results in phase III clinical trial are presented as below table.

		SKYVaricella Inj. (N=228)	Comparator (N=230)
Baseline	GMT±GSD	1.37 ± 2.62	1.22 ± 1.97
	95% CI of GMT	[1.21, 1.55]	[1.11, 1.33]
6 weeks post-vaccination	GMT±GSD	103.15 ± 2.87	54.22 ± 3.32
	95% CI of GMT	[89.89, 118.36]	[46.39, 63.38]
6 weeks post-vaccination/Baseline	GMR±GSD	75.42 ± 3.77	44.58 ± 3.69
	95% CI of GMR	[63.42, 89.69]	[37.63, 52.81]
Seroconversion rate*	% (n/N)	99.53 (211/212)	96.38 (213/221)
	95% CI of seroconversion rate	[97.40, 99.99]	[92.99, 98.42]
	Difference of rates between two vaccines	3.15	
	95% CI of difference of rates between two vaccines	[0.52, 5.78]	
*Seroconversion rate: Proportion of subjects who converted from seronegative (with FAMA VZV antibody titer <1:4) before vaccination to seropositive (with FAMA VZV antibody titer ≥ 1:4)			

3) Non-clinical information
   The results from safety pharmacology studies (cardiovascular, respiratory and central nervous systems), single and repeated dose toxicity studies, and reproductive and developmental toxicity studies showed no potential adverse effects in humans.

7. Storage

Keep refrigerated at 2°C to 8°C in a hermetic container away from light.

8. Expiration date

As marked separately on the primary container.

9. Packaging units

1) A box of 5 lyophilized vaccine vials and 5 diluent vials
2) A box of 10 lyophilized vaccine vials and a box of 10 diluent vials

10. Manufacturer

SK bioscience Co., Ltd.

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11. Importer

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