Description	SKYVaricella_PI_Malaysia
Color	K
Size(mm)	W160 X L240
Folding Size(mm)	W30 X L80

1P

VCA06AF03

30mm
접지

8X8mm
아이마크

SKY Varicella

powder and solvent for suspension for injection

Varicella Virus Vaccine (live) [Oka/SK]

pharmaniaga®

SK bioscience

Controlled Medicine | **Subcutaneous Inj.**

Name of Medicine
SKYVaricella powder and solvent for suspension for injection

Active Ingredient
After reconstitution,each dose (0.5ml) contains:
Live, attenuated varicella-zoster virus[1]
(Virus strain: Oka/SK, Cell Line: MRC-5) 2,400 - 40,000 PFU

[1] produced in human diploid cells (MRC-5)
[2] PFU = Plaque-forming units

Excipient
Powder
Other ingredients: Sucrose, Hydrolyzed gelatin, Urea, Monosodium glutamate, Disodium edetate, L-cysteine, Glycine, Sodium dihydrogen phosphate dihydrate, Disodium phosphate dodecahydrate, Sodium chloride, Potassium chloride, Sodium hydroxide

Solvent/Diluent
Water for Injection

Dosage Form
Powder and solvent for suspension for injection

Product Description
Powder
Lyophilized white crystalline pellet.

Solvent/Diluent
Clear, colorless liquid.

After reconstitution: Colorless or pale-yellow liquid.

Pharmacodynamics
Mechanism of Action
Varicella (chickenpox) is caused by primary infection with the varicella-zoster virus (VZV). SKYVaricella is a live attenuated VZV vaccine (Oka/SK strain) inducing an immune response to varicella infection.

Immunogenicity results
Immunogenicity of SKYVaricella 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 (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, 53.81]
Seroconversion rate*	% (n/N)	99.53 (211/212)	96.38 (213/221)
	95% CI conversion rates	[97.40, 99.99]	[92.99, 98.42]
	Difference of rates between two vaccines	3.15	
	95% CI 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)

Pharmacokinetic
Not applicable

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

Recommended Dosage
Individuals from 12 months to 12 years of age:
Individuals should receive a single dose (approximately 0.5 mL) subcutaneously.
The need for a booster dose is not known.

Infants below 12 months of age:
No data on efficacy and safety of SKYVaricella for use in children below 12 months of age are currently available.

Method of Administration
SKYVaricella is for subcutaneous administration in the outer aspect of the upper arm (deltoid region).
SKYVaricella should not be administered intravascularly or intramuscularly.

Instruction for Use
Instructions for reconstitution of the vaccine with solvent/diluent:
- To reconstitute the vaccine, withdraw the total volume of provided solvent/diluent (0.7ml) and inject all withdrawn solvent/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 as a single dose 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.

SKYVaricella should be stored in the refrigerator and reconstituted immediately upon removal from the refrigerator. The vaccine should be used immediately after reconstitution. Do not freeze reconstituted vaccine.

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.

Route of Administration
For subcutaneous injection.

Contraindications
1) Individuals with a history of hypersensitivity reaction to gelatin or any other component in SKYVaricella.
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 including high doses of corticosteroids (SKYVaricella may cause rash or disseminated diseases in individuals with immunodeficiency or on immunosuppressive therapy, as the vaccine is live, attenuated varicella virus vaccine).
5) Individuals with untreated active tuberculosis.
6) Pregnant women or women of child-bearing potential.
7) Individuals with febrile respiratory disease or other febrile infections.
8) Individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Warnings and Precautions
1) The duration of protection against varicella infection after vaccination with SKYVaricella is unknown.
2) Effectiveness of re-vaccination has not been evaluated. The need for booster doses is not defined.
3) As with other vaccines, vaccinations with SKYVaricella does not result in protection of all vaccine recipients.
4) As with other vaccines, anaphylactic/anaphylactoid reaction might occur with SKYVaricella. Adequate treatment provisions, including epinephrine injection (1:1,000) should be available for immediate use.
5) Deferral of vaccination should be considered in acute illness (e.g. fever > 38.0°C)
6) Transmission of the virus has not been reported from SKYVaricella 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 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 woman without documented history of chickenpox or laboratory evidence of prior infection
- Newborn infants of mothers without documented history of chickenpox or laboratory evidences of prior infection

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

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

Interaction with Other Medicaments
1) No data are available on the concomitant administration of this varicella vaccine with other vaccines. However, WHO recommends that varicella vaccine can be administered concomitantly with other vaccines included in the routine childhood immunization programme. Unless given together with other live viral vaccines (measles, MR, MMR), it should be administered at a minimum interval of 28 days.
2) After blood or plasma transfusion, or administration of immune globulin or varicella-zoster immune globulin, SKYVaricella should be vaccinated with the minimum interval (3 to 11 months), depending on the type and dose of blood or immunoglobulin.
3) SKYVaricella 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 after administration of SKYVaricella unless its use outweighs the benefit of vaccination.
4) 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.

Incompatibilities
The vaccine must not be mixed with other medicinal products. The vaccine must not be reconstituted with other medicinal products except those mentioned under **Instruction for Use**.

Pregnancy and Lactation
Pregnancy
Safety of SKYVaricella has not been evaluated in pregnant women. Direct and/or indirect adverse event related to reproductive and developmental toxicity has not been observed in animal studies. However, SKYVaricella 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.

Breast-feeding
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 is administered to nursing mothers.

Fertility
No human fertility data are available. Animal data have not shown effects on female fertility. Male fertility has not been assessed in animals.

Adverse Effects

1. Clinical trial data
1) Safety of SKYVaricella 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, irritability, somnolence 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 are summarized in below table. Frequencies are reported as:
Very common (≥1/10) /Common (≥1/100 to <1/10) /Uncommon (≥1/1,000 to <1/100) /Rare (≥1/10,000 to <1/1,000) /Very rare (<1/10,000)

Phase II clinical trial (N=114)

	System Organ Class	Adverse Drug Reactions	Frequency
Local reaction	General disorders and administration site conditions	Pain/tenderness	Very common
		Induration/swelling	Common
	Skin and subcutaneous tissue disorders	Erythema/redness	Very common
Systemic reaction	General disorders and administration site conditions	Fever	Common
		Fatigue/malaise[1]	Very rare
	Nervous system disorders	Somnolence	Common
		Headache	Common
	Psychiatric disorders	Irritability	Very common

[1]Fatigue/malaise was investigated for children aged 5 years and older. (Phase II clinical trial N=0/9)

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2P

Phase III clinical trial (N=251)

	System Organ Class	Adverse Drug Reactions	Frequency
Local reaction	General disorders and administration site conditions	Pain/tenderness	Very common
		Induration/swelling	Very common
	Skin and subcutaneous tissue disorders	Erythema/redness	Very common
Systemic reaction	General disorders and administration site conditions	Fever	Common
		Fatigue/malaise[1]	Very common
	Nervous system disorders	Somnolence	Common
		Headache	Common
	Psychiatric disorders	Irritability	Very common

[1]Fatigue/malaise was investigated for children aged 5 years and older. (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. The most frequently reported unsolicited adverse drug reactions 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.

Phase II clinical trial (N=114)

System Organ Class	Adverse Drug Reactions	Frequency
Gastrointestinal disorders	Vomiting	Uncommon
	Diarrhea	Uncommon
Infections and Infestations	Gastroenteritis	Common
	Nasopharyngitis	Common

Phase III clinical trial (N=251)

System Organ Class	Adverse Drug Reactions	Frequency
Gastrointestinal disorders	Vomiting	Uncommon
Infections and Infestations	Upper respiratory tract infection	Very rare
General disorders and administration site conditions	Vaccination site erythema	Uncommon
Metabolism and nutrition disorder	Decreased appetite	Uncommon
Skin and subcutaneous tissue disorders	Erythema	Uncommon
	Rash	Uncommon
	Rash vesicular	Common

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, 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, 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 could not be ruled out.

2. *Adverse drug reactions reported during post-marketing use*

In addition to the adverse drug reactions reported in the clinical trials, the following adverse drug reactions have been spontaneously reported during post-marketing use of this vaccine.

① Infections and infestations

Herpes zoster, varicella

* While herpes zoster might occur post-vaccination in high-risk individuals, the incidence rate is equivalent or lower compared to unvaccinated individuals post- wild-type varicella infection.

② Vascular disorders

Shock

Post Marketing Surveillance in South Korea

During 4-year post marketing surveillance (PMS) among 623 subjects for re-examination, incidence rate of adverse events was reported by 42.22% (263/623 subjects, 514 cases) regardless of the causal relationship with SKYVaricella Inj. Serious adverse drug reactions and unexpected adverse drug reactions of which causal relationship with SKYVaricella Inj. could not be ruled out are shown in below table according to its incidence frequency.

	Adverse Drug Reactions	Frequency[1]
Infections and infestations	Acute sinusitis	Uncommon
Injury, poisoning and procedural complications	Scratch	Uncommon

[1]Acute sinusitis and scratch are the unexpected adverse drug reactions, each of which was reported by 0.16% (1/623 subjects.)

Overdose and Treatment

Administration of higher than recommended dose of SKYVaricella Inj. was not evaluated in the clinical studies.

Accidental administration of more than the recommended dose of varicella vaccine has been reported (either a larger dose than recommended was injected, more than one injection was given, or the interval between injections was shorter than that recommended). Of these cases, the following adverse events were reported: injection-site redness, soreness, inflammation; irritability; gastrointestinal complaints (i.e., hematemesis, fecal emesis, gastroenteritis with vomiting and diarrhoea); cough and viral infection. None of the cases had long-term sequelae.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

Preclinical Safety Data

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 events in humans.

Instruction for Use

Refer to Recommended Dosage

Storage Conditions

Keep both lyophilized vaccine and solvent / diluent refrigerated at 2°C to 8°C in a hermetic container away from light. Both lyophilized and reconstitued vaccine should be protected from light.

After reconstitution: 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.

Shelf Life

Powder: 24 months

Solvent/Diluent: 36 months

After reconstitution: 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.

Dosage Forms and Packaging Available

Pack size of 5

A box of 5 lyophilized vaccine vials and 5 solvent/diluent vials.

Pack size of 10

A box of 10 lyophilized vaccine vials and a box of 10 solvent/diluent vials.

Manufacturer

SK bioscience Co., Ltd., Andong plant, 150, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, 36618, Republic of Korea.

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