VZA06AF02

pharmaniaga

SKY Zoster

powder and solvent for suspension for injection

Zoster Virus Vaccine (live) [Oka/SK]

SK bioscience

Controlled Medicince / Ubat Terkawal | Subcutaneous Inj.

COMPOSITION

Each 0.5 mL of reconstituted vaccine contains:

Active ingredients:

Live, attenuated varicella-zoster virus (In-house) ..... 27,400 - 164,500 PFU
(Virus strain: Oka/SK, Cell line: MRC-5)

Excipients (Stabilizers):

Sucrose (Ph. Eur.) ..... 25.00 mg
Hydrolyzed gelatin (NF) ..... 12.50 mg
Urea (NF) ..... 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

DESCRIPTION

Powder

Lyophilized white crystalline pellet.

Solvent/Diluent

Clear and colorless liquid.

After reconstitution: Colorless or pale yellow liquid.

PHARMACODYNAMICS

Mechanism of Action

Shingles, or herpes zoster, is a painful skin rash that is caused by a reactivation of the varicella-zoster virus (VZV) , which also causes chickenpox. Clinical VZV reactivation occurs as a result of reduction in the VZV-specific immunity, which is observed with increasing age. SKYZoster prevents shingles in adults aged 50 years and older by boosting VZV-specific immunity.

Immunogenicity results

In phase III clinical study, immune responses to vaccines was evaluated in a total of 812 subjects (SKYZoster group: 407 subjects and Comparator (Zostavax) group: 405 subjects), which were included in Per Protocol Set (PPS) population. The glycoprotein enzyme-linked immunosorbent assay (gpELISA) was used to analyze geometric mean titer (GMT) and geometric mean ratio (GMR) at 6 weeks post-vaccination. The results were found to meet the immunogenicity and non-inferiority hypotheses as shown in below table.

VZV antibody titer by gpELISA		SKYZoster	Comparator (Zostavax)	GMT or GMR ratio 95% C.I.
Baseline	n	407	405	
	adjust GMT†±SE	499.47 ± 1.04	547.06 ± 1.04	0.91 ± 1.06
	95% C.I.	(458.20 , 544.45)	(502.14 , 595.99)	(0.81 , 1.02)
Week 6	n	407	405	
	adjust GMT‡±SE	1,346.37 ± 1.03	1,674.94 ± 1.03	0.80 ± 1.04
	95% C.I.	(1,273.99 , 1,422.87)	(1,585.35 , 1,769.58)	(0.75 , 0.87)
Week 6/Baseline	n	407	405	
	adjust GMR±SE	2.71 ± 1.03	3.37 ± 1.03	0.80 ± 1.04
	95% C.I.	(2.56 , 2.86)	(3.19 , 3.56)	(0.75 , 0.87)

†adjust GMT: GMT adjusted for age and sex and by covariate
‡adjust GMT: GMT adjusted for age, sex and baseline titer by covariate

Furthermore, cell-mediated immune (CMI) response to VZV was analyzed in 20% sub-set subjects (SKYZoster group: 78 subjects and Comparator (Zostavax) group: 83) using the enzyme-linked immunospot (ELISPOT) of Interferon-gamma Enzyme-Linked Immunospot (IFN-γ ELISPOT) and Interleukin-2 Enzyme-Linked Immunospot (IL-2 ELISPOT) and the results are presented in below tables.

VZV-CMI response by IFN-γ ELISPOT		SKYZoster	Comparator (Zostavax)	GMC or GMR ratio 95% C.I.
Baseline	n	78	83	
	GMC±SD	46.29 ± 3.37	43.84 ± 3.21	1.06 ± 3.29
	95% C.I.	(35.20 , 60.88)	(33.99 , 56.54)	(0.73 , 1.53)
Week 6	n	78	83	
	GMC±SD	95.60 ± 2.43	91.11 ± 2.30	1.05 ± 2.36
	95% C.I.	(78.23 , 116.83)	(76.00 , 109.24)	(0.80 , 1.37)
Week 6/Baseline	n	78	83	
	GMC±SD	2.07 ± 2.48	2.08 ± 2.31	0.99 ± 2.39
	95% C.I.	(1.68 , 2.53)	(1.73 , 2.49)	(0.76 , 1.30)

VZV-CMI response by IL-2 ELISPOT		SKYZoster	Comparator (Zostavax)	GMC or GMR ratio 95% C.I.
Baseline	n	78	83	
	GMC±SD	4.61 ± 7.06	3.95 ± 7.10	1.17 ± 7.08
	95% C.I.	(2.97 , 7.17)	(2.57 , 6.06)	(0.64 , 2.15)
Week 6	n	78	83	
	GMC±SD	17.37 ± 5.56	13.59 ± 6.33	1.28 ± 5.95
	95% C.I.	(11.80 , 25.57)	(9.08 , 20.34)	(0.73 , 2.23)
Week 6/Baseline	n	78	83	
	GMR±SD	3.76 ± 4.63	3.44 ± 4.30	1.09 ± 4.46
	95% C.I.	(2.66 , 5.32)	(2.50 , 4.74)	(0.69 , 1.74)

PHARMACOKINETICS

Not applicable

INDICATIONS

Prevention of herpes zoster (shingles) in individuals aged 50 years and older.

RECOMMENDED DOSAGE

Posology

Individuals should receive a single dose (approximately 0.5 mL) subcutaneously. The need for a booster dose is not known.

Pediatric population

SKYZoster should be administered only for prevention of herpes zoster (shingles) in individuals aged 50 years and older. No data are available for pediatric population. SKYZoster is not indicated for prevention of primary varicella infection (Chickenpox) and should not be used in children and adolescents.

Method of Administration

Administer total reconstituted vaccine volume (approximately 0.5mL) as a single dose subcutaneously in the deltoid region of the upper arm. Do not inject intravascularly or intramuscularly.

Instruction for Use

- To reconstitute the vaccine, inject the entire content of the provided solvent/diluent (0.7 ml) into the vial of lyophilized vaccine using enclosed 23G needle.
- Gently agitate to dissolve completely.
- Withdraw the entire content (approximately 0.5 mL) of the reconstituted vaccine and inject the vaccine subcutaneously using enclosed 25G needle.
- The vaccine should be administered immediately after reconstitution, in order to minimize loss of potency.
- Discard reconstituted vaccine, if not used within 30 minutes.

SKYZoster should be reconstituted immediately upon removal from the refrigerator. After reconstitution, the vaccine should be used right away or up to 30 minutes when stored at room temperature. Do not freeze reconstituted vaccine.

To reconstitute and administer this vaccine, use the needles provided in the package. Dispose used needles appropriately to prevent being re-used to other individuals.

ROUTE OF ADMINISTRATION

Subcutaneous injection.

CONTRAINDICATIONS

1) Individuals with a history of hypersensitivity reaction to gelatin or any other component in SKYZoster.
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-dose corticosteroids). However, SKYZoster is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or in patients who are receiving corticosteroids as replacement therapy for adrenal insufficiency. SKYZoster may cause disseminated diseases in individuals with immunodeficiency or on immunosuppressive therapy, as the vaccine is live, attenuated zoster virus vaccine.
5) Individuals with untreated active tuberculosis.
6) SKYZoster should not be administered to women who are or may be pregnant.
7) SKYZoster is not indicated for prevention of primary varicella infection (Chickenpox) and should not be used in children and adolescents.

ADVERSE EVENTS

The median age of subjects enrolled in the clinical studies (N=845), whom were administered with SKYZoster was 59 years. Of the subjects, 440 were 50-59 years of age, 298 were 60-69 years of age and 107 were 70 years and older. A total number of elderly subjects more than 65 years of age was 229.

1) Local (injection site) reaction: Pain, erythema/redness, and induration/swelling may occur.
2) Systemic reaction: Myalgia, fatigue/ malaise, headache, diarrhea, vomiting and fever may occur after vaccination.
3) Safety of SKYZoster was evaluated in 842 subjects aged 50 years and older and 401 subjects (47.62%) experienced adverse drug reactions.

① Solicited adverse drug reaction† (local and systemic reactions) are summarized in below table.

		Total (N=842)	Phase I clinical trial (N=90)	Phase II/III clinical trial (N=340)	Phase III clinical trial (N=412)
Local reaction	Erythema/redness	24.35%	30.00%	22.65%	24.51%
	Pain	22.92%	17.78%	27.94%	19.90%
	Induration/swelling	9.98%	12.22%	12.06%	7.77%
Systemic reaction	Myalgia	16.75%	23.33%	14.41%	17.23%
	Fatigue/malaise	16.39%	20.00%	17.94%	14.32%
	Headache	8.31%	10.00%	9.12%	7.28%
	Diarrhea	2.73%	3.33%	3.82%	1.94%
	Vomiting	0.83%	0.00%	1.47%	0.49%
	Fever	0.59%	0.00%	1.18%	0.24%

† Adverse drug reactions were reported as per the clinical study protocols. The safety information of solicited adverse drug reactions was collected for 6 weeks post-vaccination in phase I clinical trial (N=90) and 5 days post-vaccination in phase II/III and III clinical trials (N=752).

② Unsolicited adverse drug reactions were reported in 19 (2.26%) out of 842 subjects during 6 weeks post-vaccination of SKYZoster. The most frequently reported unsolicited adverse drug reaction was skin and subcutaneous tissue disorders with 6 subjects (0.71%) reporting 7 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%) during the study period are shown below.

Disorders	Details
Respiratory, Thoracic and Mediastinal Disorders	Nasopharyngitis, upper respiratory tract infection
Skin and Subcutaneous Tissue Disorders	Pruritus, rash, erythematous rash, pruritus rash, rash vesicular, skin lesion, drug eruption
Psychiatric Disorders	Insomnia
Nervous System Disorders	Dreamy state, somnolence, dizziness, headache
Musculoskeletal and Connective Tissue Disorders	Musculoskeletal stiffness
Gastrointestinal Disorders	Nausea
Vascular Disorders	Vasculitis
General Disorder and Administration Site Conditions	Injection site pruritus
Ear and Labyrinth Disorders	Ear pain

③ 6 cases of serious adverse events were reported in 6 (0.71%) out of 842 subjects during 6 weeks post-vaccination reporting period (gastric cancer, bronchitis, contusion, lower limb fracture, pancreatitis, ligament sprain). All of these serious adverse events were determined to have no causal relationship with SKYZoster.

④ Varicella-like and zoster-like rashes were diagnosed in 3 out of 842 subjects vaccinated with SKYZoster during 6 weeks post-vaccination reporting period and their causal relationship with SKYZoster could not be ruled out. In phase I clinical trial, no subjects from the SKYZoster group and comparator (Zostavax®) group reported varicella-like or zoster-like rash during 6 weeks post-vaccination reporting period. In phase II/III clinical trial, 2 subjects reported varicella-like and zoster-like rash within 6 weeks post-vaccination. The specimen acquired from the subjects with zoster-like rash could not be determined as the specimen was inadequate for Polymerase Chain Reaction (PCR) testing. From the PCR testing result of the varicella-like rash specimen, varicella-zoster virus was detected, but not able to determine the virus strain (wild type or Oka/SK strain).

In phase III clinical trial, one subject from each SKYZoster and comparator (Zostavax®) group reported varicella-like and zoster-like rashes. Of the reported cases, one case of varicella-like rash was reported in the SKYZoster group and while the PCR testing detected varicella-zoster virus, it could not determine the virus strain (wild type or Oka/SK strain). The PCR testing on one case of zoster-like rash reported in comparator (Zostavax®) group also detected varicella-zoster virus, but the virus strain (wild type or Oka/Merck) could not be determined.

⑤ Post Marketing Experience in South Korea
During 4-year post marketing surveillance (PMS) among 651 subjects for re-examination in South Korea, incidence rate of incidence rate of adverse events was reported by 11.67% (76/651 subjects, 121 cases) regardless of the causal relationship with SKYZoster. No serious adverse drug reactions of which a causal relationship with the SKYZoster could not be ruled out are shown below according to its frequency.

System Organ Class (SOC)	Unexpected adverse drug reactions were reported by 1.08% (7/651 subjects, 7 cases)
Musculoskeletal and Connected Tissue Disorders	Back pain
General Disorders and Administration Site Conditions	Chills, Vaccination site discolouration
Skin and Subcutaneous Tissue Disorders	Urticaria, Dermatitis contact

⑥ Analysis and assessment of post marketing adverse events in South Korea
Analysis and assessment of signal was conducted by comparing the adverse events from the post-marketing surveillance of SKYZoster wit the post-marketing adverse events (Including adverse events from post-marketing surveillance) reported from all of licensed medicines in South Korea (1989-Dec 31, 2021), and the adverse event identified to occur more frequently in SKYZoster is as follows. However, this does not mean that the casual relationship between the component of this vaccine and the following adverse event has been proved.
* General disorders and administration site conditions: Chills

WARNINGS AND PRECAUTIONS

1) The physicians should interview a recipient on post-vaccination experiences of live, attenuated varicella virus vaccine, before administrating SKYZoster.
2) SKYZoster should be administered only for prevention of herpes zoster (shingles) in individuals aged 50 years and older.
3) SKYZoster is not indicated for prevention of primary varicella infection (Chickenpox).
4) SKYZoster should be administered only to a recipient who can induce an adequate immune response.
5) SKYZoster is not indicated for treatment of zoster or post-herpetic neuralgia.
6) As with other vaccines, serious adverse reactions, including anaphylaxis, might occur with SKYZoster. Adequate treatment provisions, including epinephrine injection (1:1,000), should be available for immediate use.
7) Deferral should be considered in acute illness (for example, in the presence of fever, > 38.0°C).
8) As with other vaccines, vaccination with SKYZoster does not result in protection of all vaccine recipients.
9) Effectiveness of the multiple-dose of SKYZoster has not been evaluated. The need for a boost dose is not defined.
10) Transmission of the vaccine virus has not been reported from SKYZoster clinical studies. However, with live, attenuated varicella-zoster virus (VZV) vaccines, transmission of vaccine virus may occur rarely between vaccinees with breakthrough infections and susceptible contacts.

Pediatric use
No data are available for pediatric population.

INTERACTION WITH OTHER MEDICAMENTS
Concurrent administration of SKYZoster and anti-viral medications known to be effective against VZV has not been evaluated.

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

PREGNANCY AND LACTATION
The safety of SKYZoster in pregnant women and breast-feeding women has not been assessed in clinical trials.

Pregnancy:
Safety of SKYZoster has not been evaluated in pregnant women. Direct and/or indirect adverse event related to reproduction and developmental toxicity has not been observed in animal studies. However, SKYZoster should not be administered to pregnant women since naturally occurring VZV infection is known to sometimes cause fetal harm. Pregnancy should be avoided for 3 months following administration of SKYZoster.

Lactation
It is not known whether varicella-zoster virus is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if SKYZoster is administered to a nursing woman.

Fertility
SKYZoster has not been evaluated in fertility studies.

OVERDOSE AND TREATMENT
Administration of a higher than recommended dose of SKYZoster was not evaluated in the clinical studies.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive or use machines have been performed.

PRECLINICAL SAFETY DATA
Non-clinical data revealed no special hazard based on conventional repeat dose toxicity studies. SKYZoster was well tolerated and immunogenic in rats. In a repeat-dose toxicity study, 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 rats.

STORAGE
Keep both lyophilized vaccine and solvent / diluent refrigerated at 2°C to 8°C in a hermetic container away from light.
After reconstitution: The vaccine should be administered immediately after reconstitution, in order to minimize loss of potency. Discard reconstituted vaccine, if not used within 30 minutes.

EXPIRATION DATE
As marked separately on the primary container.

PACKAGING UNITS
A package contains 1 single-dose vial of lyophilized vaccine, 1 prefilled syringe of diluent (0.7mL) and 2 sterilized disposable needles (23G and 25G).

PRODUCT REGISTRATION HOLDER
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