Summary of Product Characteristics for Pharmaceutical Products

1. Name of the Medical Product

General name: Varicella Vaccine, Live

It is a suspension for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted by using the accompanying excipient diluent (sterile WFI) of 0.5 mL.

2. Quality and Quantitative Composition

Each 0.5 mL/vial after reconstitute:
Live attenuated Varicella-herpes zoster virus (Oka strain) [1, 2, 3] titer:

- For release: 4.0 ~ 4.8 lg PFU/mL
- For shelf life: 3.6 ~ 4.8 lg PFU/mL

[1] produced in human diploid (SV-1) cells
[2] international standard virus strain purchased from ATCC
[3] the virus titer is tested using an in-house reference

Excipient(s):
There is no anti-microbial preservative, gelatin and antibiotic used in this vaccine. For a full list of excipients, please refer to section 6.1.

3. Pharmaceutical Form

Varicella Vaccine, Live is a suspension for injection supplied as a white and loose lyophilized vaccine, after reconstitution using the accompanying excipient diluent (sterile WFI), it is a clear colourless to opalescence liquid.

4. Clinical Particulars

4.1 Therapeutic Indication

0.5 mL dose is indicated for active immunization against infection caused by varicella in individuals aged 1 year (12 months) to 12 years (before 13th birthday).

4.2 Posology and Method of Administration

Posology
Recommended dosage and schedule are presented as below:

Age group	Dosage	Injection Route
>1 but <12 years old	0.5 mL after reconstitution	Subcutaneous injection

One dose for primary immunization. In addition, one dose of booster vaccination can be drawn from experience with epidemiological data and clinical research, or based on the needs of local epidemic control.

Method of Administration

The vaccine could only be administrated by subcutaneous injection at the low border of the lateral deltoid of upper arm.

The process of preparation

The vaccine is administrated after reconstitution by using the sterile diluent (WFI) supplied with it. Use a standard suitable syringe to transfer the entire ampoule diluent into the vaccine vial. Shake the vaccine to allow a proper reconstitution.

4.3 Contraindication

Allergic reaction

Subjects with known allergic reaction to any component of the vaccine, including excipients.

Concurrent illness

Do not administer Varicella Vaccine, Live to individuals with any acute illness, severe chronic diseases, and acute stage of a chronic disease or febrile illness.

4.4 Special Warning and Precautions for use

- Adequate treatment provisions, including epinephrine injection and emergency treatment, should be available for immediate use. Individuals should be observed for at least 30 minutes on site after receiving Varicella Vaccine, Live.

- Individuals with history or family history of convulsions, chronic diseases, epilepsy, allergic constitution, or lactating women, should be administered under the guidance of doctors.

- If cardiogenic reaction occurs during administration of similar vaccines, vaccination of Varicella Vaccine, Live should be concerned.

- Vaccination should be deferred at least 3 months following administration of immune globulins, avoiding affect the immune effect.

- Vaccination should be deferred one-month following the use of other live

attenuated vaccines.

- Varicella Vaccine is not recommended during an epidemic of varicella.

- Avoid exposing Varicella Vaccine, Live to disinfectant during use.

- Avoid the use of Varicella Vaccine, Live under these conditions:
· Container abnormalities, such as crack;
· Illegible label or expired;
· Incomplete reconstitution or turbidity after reconstitution;
· Other abnormal appearance.
- Do not administer Varicella Vaccine, Live by intradermal injection, intravascularly or intramuscularly.

- Do not combine Varicella Vaccine, Live with any other vaccine through reconstitution or mixing.

- To minimize the loss of potency, administer Varicella Vaccine, Live immediately after reconstitution. Discard if the reconstituted vaccine is not used within 30 minutes.

- Fertile women should avoid becoming pregnant for at least 3 months after administration of Varicella Vaccine, Live.

- The transmission of vaccine virus may occur rarely, but any healthy susceptible individuals, especially those who develop a varicella-like rash 2 or 3 weeks after administration of Varicella Vaccine, Live, should attempt to avoid whenever possible close contact with pregnant women (in particular, pregnant women during the first three months of pregnancy), leukemia patients susceptible to severe varicella, and individuals receiving immunosuppressive therapy.

- Avoid use of salicylates or salicylate-containing products for 6 weeks following Varicella Vaccine, Live administration.

- Do not freeze the reconstituted vaccine.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

No studies have been conducted on Varicella Vaccine, Live interaction with other medicinal products. It is not known whether Varicella Vaccine, Live can interact with other medicinal products.

4.6 Pregnancy and Lactation

Pregnancy

Animal reproduction studies have not been conducted with Varicella Vaccine, Live. In theory, it may cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. If vaccination of post-pubertal females is undertaken, pregnancy should be avoided for at least three months following vaccination.

Lactation

It is not known whether Varicella Vaccine, Live is excreted in human milk. Because many drugs excreted in human milk, it should be given to a lactating woman only if clearly needed after consult a doctor.

4.7 Effects on Ability to Drive and Use Machine

There are no clinical or scientific data for effects on ability to drive and use machine.

4.8 Undesirable Effects

Clinical trials experience

Vaccine-related adverse reactions reported during clinical trials are summarized below. In clinical trials, a total of 7,461 subjects were enrolled and Varicella Vaccine was administered to 4,223 participants. All subjects were monitored for up to 30 days after a single dose of Varicella Vaccine, Live; in addition, most of the subjects were monitored for up to 180 days for long-term safety evaluation.

Adverse reactions mentioned in clinical trials reports are classified using grading standard form Council for International Organizations of Medical Sciences (CIOMS).

Very common	≥ 10%
Common	1%-10%, 1% was inclusive
Uncommon	0.1%-1%, 0.1% was inclusive
Rare	0.01%-0.1%, 0.01% was inclusive
Very rare	<0.01%

Systemic adverse reactions

Very common: fever (13.95%)

Uncommon: diarrhea, cough, nausea/vomiting, headache, fatigue/malaise, allergic reaction, rhinorrhea;
Rare: abdominal pain, muscle pain, dizzy, anaphylactoid purpura, upper respiratory tract infection, herpes virus infection;

Local adverse reactions

Uncommon: redness, pain, swelling, rash, itch;
Rare: induration.

Severe adverse reaction

During the clinical trial, there was one severe adverse reaction occurred, which was anaphylactoid purpura and recovered after treatment.

Post-Marketing Experience of Congeneric Product Overseas

No post-marketing data for this product at this point. Adverse reactions from other licensed varicella vaccines are summarized as follows:

Systematic adverse reactions

Viral infections, varicella erythema, pain, bacterial infections, fungal infections, depression, hypersensitivity reactions, anaphylaxis (including anaphylactic shock), angioneurotic edema, facial edema, and peripheral edema.

Digestive system

Indigestion.

Hemic and lymphatic system

Lymphadenopathy, thrombocytopenia, aplastic anemia.

Infections and Infestations

Viral encephalitis, herpes zoster and varicella (caused by wild type varicella virus infection after vaccination).

Nervous/Psychiatric

Toothache, neuroticism, lethargy, irritability, convulsion, stroke, cerebellar ataxia, meningitis, acute disseminated encephalomyelitis, transverse myelitis, Guillain-Barre syndrome, Bell's paralysis.

Respiratory

Upper respiratory diseases, pharyngitis, rhinitis, asthma, sinusitis,

pneumonia, respiratory disorders, dyspnea.

Skin

Itching, eczema, purpura, sweat gland disease, xeroderma, urticaria, unexplained Steve-Johnson syndrome and erythema multiforme.

The following adverse reactions are also observed in post-marketing use of other attenuated virus vaccines:

Lymph node enlargement at the injection site;

Allergic/anaphylactic reactions caused by any components of the vaccine: allergic rash, thrombocytopenic purpura and anaphylactic shock;

Convulsions (with or without fever), etc.

The adverse reactions mentioned above should be paid attention in the post-marketing use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the PPB website https://pv.pharmacyboardkenya.org.

4.9 Overdose

N.A.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Viral vaccine, ATC code: J07BK01.

Varicella Vaccine, Live confers immunity against VZV by inducing antibody titers greater than those obtained after passive immunization with immunoglobulin. Antibody appear shortly after one dose injection and 30 days after vaccination, the seropositive rates were 99.43% (≥ 1:4) and 96.28% (≥ 1:8); the seroconversion rates were 97.13% (≥ 1:4) and 94.27% (≥ 1:8); the GMT was 1:46.48; and the GMI was 6.91.

5.2 Pharmacokinetic Properties

Not applicable to vaccine for prophylaxis.

5.3 Preclinical Safety Data

In accordance with the requirements of the General Principles for Technical Review of Preclinical Safety Evaluation of Preventive Biological Products, sufficient toxicity studies in non-clinical research stages have been conducted on Varicella Vaccine, Live, including an acute toxicity test in mice, a systemic active allergy test in guinea pigs and a local irritation test in rabbits. The results are as follows:

5.3.1 Acute toxicity test of Varicella Vaccine, Live by subcutaneous injection in mice

After a single subcutaneous injection of Varicella Vaccine, Live, the mice were observed for 14 days. During the observation period, all mice in the negative control group and the test article group survived with normal food intake, and no abnormality was observed in the animal status; each group of animals had normal weight growth, and no significant difference was found between the test article group and the negative control group. After the end of the observation period, each mouse was necropsed, and no macroscopical abnormality was observed in the tissues and organs.

Therefore, under the conditions of this test, after ICR mice were subcutaneously injected with 0.5 ml of reconstituted bulk of Varicella Vaccine, Live, no significant toxic reactions were observed, and the no-observed-adverse-effect level (NOAEL) was greater than 25 ml/kg BW, which was 500 times the clinical dose.

5.3.2 Systemic active allergy test in guinea pigs

Varicella Vaccine, Live was subcutaneously injected for sensitizing and then intravenously injected for challenging. Observation showed that none of the animals in the test article group and the negative control group presented with symptoms of allergic reactions, the allergic reactions were evaluated as negative, and the incidence of allergic reactions was 0%; all animals in the positive control group had allergic reactions, the allergic reactions were evaluated as extremely strong positive, and the incidence of allergic reactions was 100%.

Therefore, under the conditions of this test, guinea pigs had negative systemic active allergic reactions to Varicella Vaccine, Live.

5.3.3 Muscle irritation test in rabbits

Eight large-eared white rabbits were selected, and the left and right sides

of the same rabbit were injected once with Varicella Vaccine, Live 0.5 ml per rabbit for self-comparison. The animals were observed with naked eyes at 48 hours and on Day 16 after administration. No significant abnormal changes were found in the test article group or the negative control group; histopathological examination was performed at 48 hours and on Day 16 after administration, and no abnormal pathological changes were found in the negative control group or the test article group.

Therefore, under the conditions of this test, after Varicella Vaccine, Live reconstituted bulk was intramuscularly injected once at 0.5 ml per animal, no irritant reactions caused by the drug were observed at the injection site of the quadriceps femoris of the rabbits tested.

5.3.4 Long-term toxicity test data in rats

Sinovac (Dalian) entrusted JOINN Laboratories (China) Co., Ltd. with GLP qualification to perform a toxicity test and immunogenicity test of Varicella Vaccine, Live and cell matrix administered by repeated subcutaneous injection to SD rats for 4 weeks with a recovery period of 6 weeks. The test results showed that the animals in each group did not present with symptoms of vaccine-related toxicity during the test period. No regular changes of toxicological significance were found in the body weight, food intake, body temperature, blood cell count, coagulation function, blood biochemistry, ophthalmological examination, T lymphocyte subset distribution, cytokine detection or testing of the number of IFN-γ-secreting lymphocyte spots in PBMCs in each main test group of animals. The antibody test results showed that with the increase of administration frequency and doses, the antibody level of the animals in the vaccine group showed an increasing trend, and the serum antibody titer of the animals in each group did not decrease significantly at the end of recovery. The results of pathological examination showed that there were no significant changes related to the administration in the organ weights or organ coefficients of the animals in each group. No significant pathological changes of systemic toxicity related to the administration were macroscopically and microscopically found in all tissues or organs. No significant irritant reactions related to the test article were found at the local injection tissue. Therefore, after Varicella Vaccine, Live was administered to SD rats repeatedly by subcutaneous injection at a dose of 1 or 5 doses per animal once every 2 weeks for 3 consecutive times, no significant systemic toxicity reaction was observed, and the safe dose was 5 doses per animal. This dose was much higher than the proposed clinical dose.

To sum up, the results of toxicity test and immunogenicity test of Varicella Vaccine, Live and cell matrix administered by repeated subcutaneous injection to SD rats for 4 weeks with a recovery period of 6 weeks met the

provisions.

5.3.5 Toxicity test of Varicella Vaccine, Live administered by repeated subcutaneous injection to cynomolgus monkeys for 6 weeks with a recovery period of 6 weeks

Sinovac (Dalian) entrusted JOINN Laboratories (China) Co., Ltd. with GLP qualification to perform a toxicity test of Varicella Vaccine, Live administered by repeated subcutaneous injection to cynomolgus monkeys for 6 weeks with a recovery period of 6 weeks. The test results showed that no regular changes of toxicological significance were found in the clinical observation, body weight, body temperature, ECG parameters, ophthalmological examination, hematology, coagulation function, blood biochemistry, urinalysis, T lymphocyte subset, cytokines, number of IFN-γ-secreting lymphocyte spots in PBMCs or other indicators in each group of animals during the test period. The results of pathological examination showed that there were no changes related to the administration in the organ weights or organ coefficients of the animals in each group. The gross and histopathological examinations of the animals in each group showed no pathological changes of systemic toxicity related to the administration.

Therefore, after Varicella Vaccine, Live was administered by repeated subcutaneous injection to cynomolgus monkeys once every 3 weeks for 3 consecutive times, no vaccine-related systemic toxicity reaction was observed in each group of animals, and the safe dose was 5 doses per animal. Varicella Vaccine, Live is immunogenic to cynomolgus monkeys.

Safety pharmacology was well evaluated through the experiments of active systemic allergy test in guinea pigs, acute toxicity test in mice, intramuscular irritation test in rabbits, and neurotoxicity test in thalamus of rhesus monkeys. The study results proved that there are neither significant toxicity was observed, nor neurotoxicity.

Long-term safety preclinical study were carried out on SD rats and cynomolgus monkeys, which indicate that there was no any potential toxicities.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sucrose	5% (g/mL)
Sodium glutamate	0.072% (g/mL)
Sodium chloride	0.228% (g/mL)
Potassium chloride	0.006% (g/mL)
Disodium hydrogen phosphate	0.628% (g/mL)

Potassium dihydrogen phosphate 0.058% (g/mL)

6.2 Incompatibilities

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

6.3 Shelf Life

The validity period of the vaccine is 24 months;
The validity period of the excipient diluent 48 months.

6.4 Vaccine Vial Monitor (VVM)

The vaccine is supplied with a VVM 14 mounted in the vial cap.

6.4 Special Precautions for Storage

Stored and shipped at 2°C and 8°C, protect from light.
The sterile diluent (WFI) is preserved in well-closed containers up to 40°C.

6.5 Nature and Contents of Container

Lyophilized cake (approximately 0.5 mL after reconstitution) in a vial (neutral borosilicate glass) with stopper (brominated butyl rubber) and cap (aluminum-plastics combinations) in pack size of 1, including an ampoule of excipient diluent.
One inner box contains a vial of varicella vaccine and an ampoule of diluent.
One medium pack wraps 10 inner boxes.
One carton contains 20 medium packs; one carton contains 200 inner boxes (200 vials and 200 excipient diluent).
The syringes required for administration are conventional syringes and can be disposed of in the normal syringe disposal waste stream.

7. Marketing Authorization Holder

Sinovac (Dalian) Vaccine Technology Co., Ltd.
No. 36, 2nd Life Road, DD Port, Economic and Technical Development Zone, Dalian, Liaoning Province, P.R. China

8. Marketing Authorization Numbers

9. Date of Authorization

10. Date of Revision of the Text

August 6, 2020