

DATA SHEET

Name of Medicinal Product

VARILRIX

Live attenuated varicella vaccine

Presentation

VARILRIX is a lyophilised preparation of the live attenuated OKA strain of varicella-zoster virus, obtained by propagation of the virus in MRC₅ human diploid cell culture.

VARILRIX meets the World Health Organisation requirements for biological substances and for varicella vaccines.

Each dose of the reconstituted vaccine contains not less than 10^{3.3} plaque-forming units (PFU) of the varicella-zoster virus.

VARILRIX is presented as a slightly cream to yellowish or pinkish coloured pellet in a glass vial. It also includes the excipients amino acids, human albumin, lactose, neomycin sulphate, polyalcohols. The sterile diluent, water for injections, is clear and colourless and presented in ampoules and prefilled syringes.

Clinical Particulars

Therapeutic indications

VARILRIX is indicated for active immunisation and prophylaxis against varicella in healthy infants (from the age of 9 months), children, adolescents and adults.

There are socioeconomic benefits for the more extensive use of VARILRIX in the community eg. health workers, school teachers and others exposed to children should be vaccinated with VARILRIX if there is no history of varicella. Working mothers should have their children vaccinated.

Posology and method of administration

0.5ml of reconstituted vaccine contains one immunising dose.

Children from the age of 9 months up to 12 years of age, two doses of VARILRIX administered at least six weeks apart is recommended for the benefit of enhances immune response against varicella virus.

From 13 years and up: 2 doses with an interval between doses of a minimum of 6 weeks.

Interchangeability

- A single dose of VARILRIX may be administered to those who have already received a single dose of another varicella-containing vaccine

- A single dose of VARILRIX may be administered followed by a single dose of another varicella-containing vaccine.

VARILRIX SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

VARILRIX should be administered by **subcutaneous injection** only. The upper arm (deltoid region) is the preferred site of injection.

VARILRIX must be reconstituted by adding the contents of the supplied container of diluent to the vial containing the vaccine pellet. The mixture should be well shaken until the vaccine is completely dissolved in the diluent. The entire contents of the vial are to be injected.

After reconstitution, it is recommended that VARILRIX be injected as soon as possible. If not used within the recommended timelines, the reconstituted vaccine must be discarded (see "Shelf-Life"). Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they may inactivate the virus.

Any unused product or waste material should be disposed of in accordance with local requirements.

Due to minor variations of its pH, the colour of the reconstituted vaccine may vary from a clear peach to a pink coloured solution. The diluent and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the diluent or the reconstituted vaccine.

Contraindications

As with other vaccines, the administration of VARILRIX should be postponed in subjects suffering from acute severe febrile illness. In healthy subjects the presence of a minor infection, however, is not a contraindication for vaccination.

VARILRIX is contraindicated in subjects with a total lymphocyte count less than 1200 per mm³ or presenting other evidence of lack of cellular immune competence such as subjects with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infection, or patients receiving immunosuppressive therapy (including high dose corticosteroids)..

VARILRIX is contraindicated in subjects with known systemic hypersensitivity to neomycin, but a history of contact dermatitis to neomycin is not a contraindication.

VARILRIX is contraindicated during pregnancy. Furthermore, pregnancy should be avoided for three months after vaccination (see "Pregnancy").

Special warnings and special precautions for use

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the

administration of the vaccine.

Transmission of the OKA vaccine virus has been shown to occur at a very low rate in seronegative contacts of vaccinees. However, transmission has not been confirmed to occur in the absence of vaccine-associated cutaneous lesions in the vaccinee.

The mild nature of the rash which developed in the healthy contacts indicates that the virus remains attenuated after passage through human hosts. Vaccine recipients should attempt to avoid contact with susceptible high risk individuals for up to 6 weeks, where possible.

Vaccinees who develop papulo-vesicular eruptions within the first 4 weeks post vaccination should avoid contact with patients known to be immune suppressed for the duration of the rash.

Care should be exercised in patients with serious chronic diseases (such as chronic renal failure, autoimmune diseases, collagen diseases, severe bronchial asthma).

As for other varicella vaccines, cases of varicella disease have been shown to occur in persons who have previously received VARILRIX. These breakthrough cases are usually mild, with a fewer number of lesions and less fever and cough with respect to cases in unvaccinated individuals.

VARILRIX should not be administered intradermally. VARILRIX must under no circumstances be administered intravenously.

Interactions with other medicaments and other forms of interaction

In subjects who have received immune globulins or a blood transfusion, vaccination should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired varicella antibodies.

Salicylates should be avoided for 6 weeks after varicella vaccination as Reye's Syndrome has been reported following the use of salicylates during natural varicella infection.

VARILRIX can be administered at the same time as any other vaccine. Different injectable vaccines should always be administered at different injection sites.

Inactivated vaccines can be administered in any temporal relationship to VARILRIX.

Should a measles containing vaccine not be given at the same time as VARILRIX, it is recommended that an interval of at least one month should be respected since it is recognised that measles vaccination may lead to short lived suppression of the cell mediated immune response.

Pregnancy and lactation

Pregnancy

It is contraindicated to administer VARILRIX to pregnant women, because the possible effects on foetal development are unknown. Furthermore, pregnancy should be avoided for three months after vaccination.

Lactation

There are no data regarding use in breastfeeding women.

Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

Undesirable effects

VARILRIX is a vaccine of low overall reactogenicity in all age groups.

The safety profile presented below is based on a total of 5369 doses of VARILRIX administered in monotherapy to children, adolescents and adults.

Undesirable effects reported are listed according to the following frequency:

<i>Very common:</i>	$\geq 1/10$
<i>Common:</i>	$\geq 1/100$ and $< 1/10$
<i>Uncommon:</i>	$\geq 1/1000$ and $< 1/100$
<i>Rare:</i>	$\geq 1/10000$ and $< 1/1000$
<i>Very rare:</i>	$< 1/10000$

Infections and infestations:

Uncommon: upper respiratory tract infection, pharyngitis

Blood and lymphatic system disorders:

Uncommon: lymphadenopathy

Psychiatric disorders:

Uncommon: irritability

Nervous system disorders:

Uncommon: headache, somnolence

Eye disorders:

Rare: conjunctivitis

Respiratory, thoracic and mediastinal disorders:

Uncommon: cough, rhinitis

Gastrointestinal disorders:

Uncommon: nausea, vomiting

Rare: abdominal pain, diarrhoea

Skin and subcutaneous tissue disorders:

Common: rash

Uncommon: varicella-like rash, pruritus

Rare: urticaria

Musculoskeletal and connective tissue disorders:

Uncommon: arthralgia, myalgia

General disorders and administration site conditions:

Very common: pain, redness

Common: swelling at the injection site*, fever (oral/axillary temperature $\geq 37.5^{\circ}\text{C}$ or rectal temperature $\geq 38.0^{\circ}\text{C}$)*

Uncommon: fever (oral/axillary temperature $> 39.0^{\circ}\text{C}$ or rectal temperature $> 39.5^{\circ}\text{C}$), fatigue, malaise

A trend for higher incidence of pain, redness and swelling after the second dose was observed as compared to the first dose.

* Swelling at the injection site and fever were reported very commonly in studies conducted in adolescents and adults. Swelling was also reported very commonly after the second dose in children under 13 years of age.

On average, the reactogenicity after the second dose was not higher than after the first dose.

No differences were seen in the reactogenicity profile between initially seropositive and initially seronegative subjects.

High-risk patients

There are only very limited data from clinical trials available in patients at high risk of severe varicella. However, vaccine-associated reactions (principally papulo-vesicular eruptions and fever) are usually mild. As in healthy subjects, redness, swelling and pain at the site of injection are mild and transient.

Post-marketing surveillance

Infections and infestations: Herpes zoster**

Immune system disorders: Hypersensitivity, anaphylactic reactions

Nervous system disorders: Convulsions, cerebellar ataxia**

** This reaction reported after vaccination is also a consequence of wild-type varicella infection. There is no indication of an increased risk of its occurrence following vaccination compared with wild-type disease.

In clinical studies involving more than 2000 subjects from the age of 9 months, papulo-vesicular eruptions were reported in approximately 5% of the vaccinees. Most of them occur during the first three weeks after vaccination, and the number of lesions was generally below ten. Temperature above 37.5°C (axillary) / 38°C (rectal) was reported in approximately 5% of subjects during a six week follow-up of the vaccinees. The reactogenicity after the second dose in adolescents and adults was not higher than after the first dose. No difference was seen between the reactogenicity in initially seropositive and seronegative subjects.

In a four week follow-up double-blind placebo-controlled study including 513 children between 12-30 months of age, there was no significant difference in nature or incidence of symptoms in subjects receiving vaccine or placebo.

Overdose

Cases of accidental administration of more than the recommended dose of VARILRIX have been reported. Amongst these cases, the following adverse events were reported: lethargy and convulsions. In the other cases reported as overdose there were no associated adverse events.

Pharmacological Properties

Pharmacodynamic properties

VARILRIX produces an attenuated clinically inapparent varicella infection in susceptible subjects.

Some protection may be obtained by immunisation up to 72 hours after exposure to natural varicella.

The presence of antibodies is accepted to be an indication of protection.

Pharmacodynamic Effects

Efficacy studies

The efficacy of GlaxoSmithKline (GSK)'s Oka/RIT varicella vaccines in preventing confirmed varicella disease (clinical breakthrough varicella was confirmed by, polymerase chain reaction {PCR} or exposure to a varicella case) has been evaluated in a large active controlled clinical trial in which children aged 12-22 months received one dose of VARILRIX (N = 2263) or two doses of *PRIORIX-TETRA* (N = 2279). The observed vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella after one dose of VARILRIX and after 2 doses of *PRIORIX-TETRA* (mean follow-up period 35 months) are presented in Table 1.

Table 1: Efficacy results after one dose of VARILRIX compared to 2 doses of PRIORIX TETRA

Group	N	n	Vaccine Efficacy 97.5%CI
Efficacy against confirmed Varicella of any Severity			
VARILRIX	2263	243	65.4% 57.2 – 72.1
PRIORIX-TETRA	2279	37	94.9% 92.4 – 96.6
Efficacy against confirmed Moderate or Severe Varicella			
VARILRIX	2263	37	90.7% 85.9 – 93.9
PRIORIX-TETRA	2279	2	99.5% 97.5 – 99.9

N= Number of subjects included in each group

n = Number of subjects reporting at least one event(s) in each group

In a previous study specifically designed to evaluate vaccine efficacy after one dose of VARILRIX, 10 to 30-month-old children were followed up for a period of approximately 2.5 years after vaccination. The protective efficacy was 100% against common clinical cases of varicella (≥ 30 vesicles) and 88% (95% CI: 71.0-95.2%) against any serological confirmed case of varicella (at least 1 vesicle or papule).

Effectiveness studies

Effectiveness data suggest a higher level of protection and a decrease in breakthrough varicella following two doses of vaccine than following one dose.

The effectiveness of one dose of VARILRIX was estimated in different settings (outbreaks, case-control and database studies) and ranged from 20%-92% against any varicella disease and from 86%-100% against moderate or severe disease.

The impact of one dose of VARILRIX in reducing varicella hospitalizations and ambulatory visits among children were respectively 81% and 87% overall.

Immune Response

Healthy subjects

In children aged 11 months to 21 months the seroconversion rate, when measured by ELISA (50mIU/ml) 6 weeks after vaccination, was 89.6% after one vaccine dose and 100% after the second vaccine dose.

In subjects aged 9 months to 12 years, the overall seroconversion rate, when measured by Immunofluorescence Assay (IFA) 6 weeks post-vaccination, was $> 98\%$ after one vaccine dose. In children vaccinated at 12-15 months of age, antibodies persisted for at least 7 years after vaccination with one dose.

In children aged 9 months to 6 years, the seroconversion rate, when measured by IFA 6 weeks after vaccination, was 100% after a second vaccine dose. A marked increase of antibody titres was observed following the administration of a second dose (5 to 26-fold GMT increase).

In subjects aged 13 years and above, the seroconversion rate, when measured by IFA 6 weeks after vaccination, was 100% after the second vaccine dose. One year after vaccination, all subjects tested were still seropositive.

In clinical trials, the majority of vaccinated subjects who were subsequently exposed to wild-type virus were either completely protected from clinical chickenpox or developed a milder form of the disease (i.e. low number of vesicles, absence of fever).

If primary varicella infection is delayed until adolescence or adulthood, the illness is usually more severe, and may result in complications such as pneumonia, haemorrhagic varicella, encephalitis, visceral dissemination and cosmetic sequelae from superinfection of skin lesions. Complications can occur at any age but the risk increases with age. There are insufficient data to assess the rate of protection against complications of chickenpox such as encephalitis, hepatitis or pneumonia.

High-risk patients

There are only very limited data from clinical trials available in patients at high risk of varicella. The overall seroconversion rate in these patients was found to be $\geq 80\%$.

In high-risk patients, periodic measurement of varicella antibodies after immunisation may be indicated in order to identify those who may benefit from re-immunisation.

Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical safety data

Appropriate safety tests have been performed.

Pharmaceutical Particulars

Special precautions for storage

The lyophilised vaccine should be stored in a refrigerator between $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$. The diluent can be stored in the refrigerator or at ambient temperature (maximum 25°C). The lyophilised vaccine is not affected by freezing.

When supplies of VARILRIX are distributed from a central cold store, it is good practice to arrange transport under refrigerator conditions especially in hot climates.

After reconstitution, it is recommended that the vaccine be injected as soon as possible. (see "Shelf life").

Shelf life

The shelf life of VARILRIX is 24 months from the date of manufacture if stored between temperatures of $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$. The expiry date of the vaccine is indicated on the label and packaging.

It has been demonstrated that the reconstituted vaccine may be kept for up to 90 minutes at room temperature (25°C) and up to 8 hours in the refrigerator (2°C - 8°C).

Medicine Classification

Prescription Medicine

Package Quantities

VARILRIX vaccine: monodose glass vials in packs of 1.

Diluent: glass ampoules or prefilled syringes, 0.5mL in packs of 1.

Name and Address

GlaxoSmithKline NZ Ltd
AMP Centre
Cnr Albert & Customs Street
Private Bag 106600
Downtown

Auckland
NEW ZEALAND

ph (09) 367 2900
fax (09) 367 2910

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