For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

VARILRIX

Varicella Vaccine, Live IP

1. NAME OF THE MEDICINAL PRODUCT

Varicella Vaccine, Live IP.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose (0.5 ml) of the reconstituted vaccine contains:
Live attenuated Varicella virus (OKA strain, propagated in MRC5 human diploid cells)….
not less than $10^{3.3}$ plaque-forming units (PFU)

Water for Injections IP qs 0.5 mL

This vaccine contains a trace amount of neomycin. see section *4.3 Contraindications*.

For the full list of excipients, see section *6.1 List of excipients*.

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

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder or pellet of vaccine in the vial is slightly creamy to yellowish or pinkish. The solvent contained in the syringe or in the ampoule is clear and colorless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Healthy subjects

VARILRIX is indicated for active immunisation against varicella of healthy subjects and susceptible healthy close contacts from the age of 12 months onwards.

Susceptible healthy close contacts should be immunised in order to reduce the risk of transmission of virus to high-risk patients. These include parents and siblings of high-risk patients, and medical, paramedical personnel and other people who are in close contact with varicella patients or high-risk patients.

4.2 Posology and method of administration

Posology

0.5 ml of reconstituted vaccine contains one immunising dose.

Children from 12 months up to 12 years of age inclusive

It is recommended that 2 doses of *VARILRIX* be administered to children from 12 months to 12 years of age in order to ensure optimal protection against varicella. It is preferable that the second dose be administered at least 6 weeks after the first dose but under no circumstances less than 4 weeks, after the first dose.

Adolescents 13 years of age or over and adults

Two doses are necessary for subjects from the age of 13. An interval of at least six weeks should be observed between the two doses, but in no case less than four weeks.

Interchangeability

A single dose of *VARILRIX* may be administered to subjects 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.

Method of administration

VARILRIX is intended for subcutaneous injection in the deltoid region of the arm or in the anterolateral part of the thigh.

For instructions on reconstitution of the medication before administration, see section *6.6 Special precautions for disposal and other handling*.

4.3 Contraindications

VARILRIX is contraindicated in subjects with primary or acquired immunodeficiency who have a total lymphocyte count less than 1200 per mm^3 or presenting other evidence of lack of cellular immune competence, such as subjects with leukemia, lymphomas, blood dyscrasia, clinically manifest HIV infection, or subjects receiving immunosuppressive therapy including high dose corticosteroids.

VARILRIX is contraindicated in subjects who have a history of hypersensitivity to any of the constituents in the vaccine, or to neomycin. However, a history of dermatitis following contact with neomycin is not a contraindication.

VARILRIX is contraindicated in subjects who have shown signs of hypersensitivity after previous administration of varicella vaccine.

VARILRIX is contraindicated in pregnant women. Pregnancy should be avoided for one month following vaccination (see section *4.6 Pregnancy and Lactation*).

4.4 Special warnings and precautions for use

As for other vaccines, administration of *VARILRIX* should be postponed in the event of acute febrile illness. The presence of a minor infection, however, is not a contraindication.

As for any injectable vaccine, it is recommended that an epinephrine solution be available for injection in the event of a possible anaphylactic reaction (see below, "Treatment in the event of anaphylactic reaction" under Section *4.8 Undesirable Effects*). It is generally recommended that the vaccinee be kept under medical surveillance for half an hour after vaccination.

Syncope (fainting) can occur following, or even before any vaccination, with adolescents in particular, as a psychogenic reaction to injection. This can be accompanied by several neurological signs such as transient visual disturbances, paraesthesia and tonic-clonic movements of the limbs during the recovery phase. It is important that measures are in place to avoid injuries in the event of fainting.

Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they can inactivate the attenuated viruses in the vaccine.

Available data suggest that vaccination within 72 hours of natural exposure to varicella can alter the clinical course of the disease and even prevent symptoms. The degree of protection however may be limited (see section *5.1 Pharmacodynamic properties*).

As with all vaccines, a protective immune response may not be elicited in all vaccinees. As with other varicella vaccines, cases of varicella disease have occurred in people who have previously received *VARILRIX*. These breakthrough cases are usually mild, with a fewer number of lesions and less fever as compared to cases occurring in unvaccinated individuals.

Transmission of the Oka vaccine virus has been shown to occur, but in extremely rare cases, to seronegative persons in contact with vaccinated persons who have a rash. However, transmission has not been confirmed in the absence of vaccine-related skin lesions in the vaccinee.

All contact should be avoided with pregnant women susceptible to contracting varicella (especially during the first trimester of pregnancy) and with those at high risk for developing severe varicella (such as leukemia patients or patients receiving immunosuppressive therapy), especially when the person vaccinated develops a skin

eruption within 2 to 3 weeks of immunization. If contact with these persons cannot be avoided, the potential risk of transmission of the vaccine virus should be weighed against the risk of acquiring and transmitting the wild varicella virus.

In patients receiving strongly immunosuppressive treatment, clinical varicella has appeared after vaccination. A virus resembling that of the vaccine has been detected in the vesicles. In the event of severe clinical signs, antiviral treatment is indicated.

Very few reports exist on disseminated varicella with internal organ involvement following vaccination with Oka varicella vaccine strain mainly in immunocompromised subjects.

VARILRIX must not be administered intradermally or intravascularly.

Healthy persons living in close contact with patients

To further reduce the risk of infection of high-risk subjects, it is advised that non-immune persons living in close contact with varicella patients or high-risk patients also be vaccinated. This category includes parents, brothers and sisters of high-risk subjects, medical and paramedical personnel and others who live in close contact with these patients.

4.5 Interaction with other medicaments and other forms of interaction

If tuberculin testing has to be performed, it should be carried out before or simultaneously with vaccination since it has been reported that live viral vaccines may cause a temporary depression of tuberculin skin sensitivity. As this anergy may last up to a maximum of 6 weeks, tuberculin testing should not be performed within that period after vaccination to avoid false negative results.

The administration of *VARILRIX* should be postponed for at least three months after the administration of immunoglobulins or after a blood transfusion, because the vaccination may not work properly due to passively acquired varicella antibodies.

Reye's syndrome has been reported after use of salicylates during wild varicella infections. Consequently, salicylates should not be administered in the 6 weeks following vaccination.

VARILRIX can be administered at the same time as other vaccines. Different injectable vaccines should always be administered at different injection sites. *VARILRIX* must never be mixed with other vaccines in the same syringe. Inactivated vaccines can be administered at any time relative to the time of administration of *VARILRIX*.

If *VARILRIX* is administered after the measles vaccine, an interval at least a month is recommended, as it is known that vaccination against measles can cause short-term suppression of the cellular immune response.

4.6 Pregnancy and Lactation

Pregnancy

Pregnant women should not be vaccinated with *VARILRIX*.

However, no harmful effect on the fetus has been documented after administration of vaccines against varicella to pregnant women.

Pregnancy should be avoided for one month following vaccination. Women intending to become pregnant should be advised to postpone their plans.

Vaccinated persons who develop a rash within 3 weeks after the vaccination must avoid all contact with pregnant women (particularly in the first three months of pregnancy).

Lactation

There is insufficient data on the excretion of *VARILRIX* or on the presence of antibodies against *VARILRIX* antigens in breast milk.

A risk for newborns / infants cannot be ruled out.

A decision should be made either to discontinue breastfeeding or to discontinue / abstain from vaccination with *VARILRIX*, taking into account the benefit of breastfeeding for the child with regard to the benefit of prophylaxis against Varicella for the woman.

4.7 Effects on ability to drive and use machines

It is very unlikely that the vaccine has an effect on the capacity to drive a vehicle or to use machines.

4.8 Undesirable Effects

Clinical trials

Healthy subjects

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

Undesirable effects with a suspected connection with the vaccine are listed below.

Frequencies are reported as follows:

Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000),

Class of organ systems	Frequency	Side effects
Infections and infestations	Uncommon	Upper respiratory 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	Papulo-vesicular eruptions, pruritus
	Rare	Urticaria
Musculoskeletal and systemic disorders	Uncommon	Arthralgia, myalgia
General disorders and administration site conditions	Very common	Pain, redness at the injection site
	Common	Swelling at the injection site *, fever (oral / axillary temperature≥ 37.5 °C or rectal temperature≥ 38.0 ºC) *
	Uncommon	Fever (oral / axillary temperature> 39.0°C or rectal temperature> 39.5° c), fatigue, malaise

*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 given to children under 13 years of age.

A tendency has been observed toward an increase in reactions of pain, redness and swelling between the first and the second injection.

No difference was noted in the reactogenicity profile between initially seropositive and initially seronegative subjects.

Post marketing surveillance

During post-marketing surveillance, the following additional reactions have been reported after varicella vaccination:

Class of organ systems	Frequency	Side effects
Infections and infestations	unknown **	Herpes zoster *, disseminated infection by the varicella virus

Class of organ systems	Frequency	Side effects
		(vaccine strain) with involvement of internal organs
Blood and lymphatic system disorders	unknown **	Thrombocytopenia
Immune system disorders	unknown **	Hypersensitivity, anaphylactic reactions
Nervous system disorders	unknown **	Encephalitis, cerebrovascular accident, cerebellitis, cerebellitis like symptoms (including transient gait disturbance and transient ataxia), convulsions
Vascular disorders	unknown **	Vasculitis (including Henoch Schonlein purpura and Kawasaki syndrome)
Skin and subcutaneous tissue disorders	unknown **	Erythema multiforme.

*These reactions reported after vaccinations are also a consequence of infection by the wild varicella virus. There is no indication of an increased risk of these manifestations after vaccination compared to the risk incurred with the natural disease.

** Since these events have been notified spontaneously, it is not possible to estimate their frequency reliably.

Treatment in the event of anaphylactic reaction

Procedure proposed by the "Repertoire Commente des Medicaments (Annotated Repertory of Medications)" in the event that a severe anaphylactic reaction (associated with respiratory difficulties, hypotension or shock) occurs.

Treatment is based on epinephrine (adrenalin).

Intramuscular administration is preferable to subcutaneous administration due to better resorption in the event of hypotension.

The dose of epinephrine is:
- for an adult: 0.2 to 0.5 mL of a 1/ 1000 (= 1 mg/ml) aqueous solution intramuscularly
- for a child: 0.01 mL /kg of a 1/ 1000 (= 1 mg/ml) aqueous solution intramuscularly (max. 0.3 mL)

If there is no improvement, a second dose can be administered intramuscularly after 5 minutes.

Bronchodilator in the event of bronchospasm; I.V. corticosteroids; plasma substitute in the event of shock.

4.9 Overdose

Cases of accidental administration of doses higher than the recommended dose of *VARILRIX* have been reported. Among these cases, the following effects have been reported: lethargy and convulsions. In the other reported cases of overdose, there were no related secondary effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccine, ATC code: J07BK01.

The presence of antibodies after vaccination is recognized as a sign of protection against the disease.

Efficacy in clinical studies

The efficacy of the GlaxoSmithKline (GSK) vaccines, monovalent Oka (*VARILRIX*) and *PRIORIX-TETRA* [MMRV], in preventing varicella was evaluated in a large, international randomised study that included the GSK measles-mumps-rubella combined vaccine MMR (*PRIORIX*) as the active comparator. The study was conducted in Europe, where vaccination against varicella is not routine.

Children from 12 to 22 months of age received either two doses of *PRIORIX-TETRA* at a 6-week interval or one dose of *VARILRIX*. Vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella *was shown* after a primary follow-up period of 2-years (median duration of 3.2 years). In the same study, persistent efficacy was observed during the long-term follow-up periods of 6-years (median duration of 6.4 years) and 10 years (median duration of 9.8 years). The data are presented in the table below:

Group	**Timing**	**Effectiveness against confirmed varicella of any severity**	**Efficacy against moderate or severe confirmed varicella**
VARILRIX (1 dose) N =2,487	Year 2	65.4% (97.5% CI: 57. 2, 72.1)	90.7% (97.5 % CI:85.9, 93.9)
	Year 6 [(1)]	67.0% (95% CI: 61.8, 71.4)	90.3% (95% CI: 86.9, 92.8)
	10 years	67.2% (95% CI: 62.3; 71.5)	89.5% (95% CI: 86.1; 92.1)

Group	Timing	Effectiveness against confirmed varicella of any severity	Efficacy against moderate or severe confirmed varicella
Combined vaccine against measles, mumps, rubella and chicken pox (Oka) (2 doses) N = 2,489	Year 2	94.9% (97.5% CI: 92.4, 96.6)	99.5% (97.5% CI: 97.5, 99.9)
	Year 6 (1)	95.0% (95% CI: 93.6, 96.2)	99.0% (95% CI: 97.7, 99.6)
	10 years	95.4% (95% CI: 94.0; 96.4)	99.1% (95% CI: 97.9; 99.6)

N: number of subjects enrolled and vaccinated

(l) descriptive analysis

Effectiveness

Data on effectiveness appear to indicate a higher level of protection and a lower incidence of cases of varicella in those vaccinated after two doses of varicella-containing vaccine than after a single dose.

The effectiveness of doses of *PRIORIX-TETRA* in an epidemic situation in day-care centres in Germany, where routine vaccination against varicella is recommended for children from the age of 11 months, was 91% (95% CI: 65% -98%) against the disease of any severity and 94% (95% CI: 54%-99%) against the moderate disease.

The effectiveness of a dose of *VARILRIX* was assessed in different contexts (epidemic, case analysis and database studies) and varied from 20% to 92% against any type of varicella and from 86% to 100% against the moderate or severe disease.

Immune response

In children 11 months to 21 months of age, the seroconversion rate measured with ELISA, Enzygnost, Dade Behring (50 mIU/ml) six weeks reached 89.6% after administration of one dose of vaccine, and 100% after administration of a second dose of vaccine.

In children from 9 months to 12 years of age inclusive, the seroconversion rate measured by immunofluorescence six weeks after administration of a dose of vaccine exceeded 98%.

In children from 9 months to 6 years of age, the seroconversion rate measured by immunofluorescence six weeks after administration of a second dose of vaccine was 100%. A marked increase in antibody titers was observed following administration of a second dose (5 to 26-fold GMT increase).

In subjects 13 years of age and over, the seroconversion rate measured by immunofluorescence six weeks after administration of a second dose of vaccine was 100%. One year after vaccination, all subjects tested were still seropositive.

In clinical studies, efficacy data show a higher level of protection and a reduction in the number of varicella cases appearing after administration of two doses of vaccine instead of a single dose.

Published data on the prevention of varicella within 3 days after exposure to the varicella virus are limited. In a randomized, double-blind, placebo-controlled study involving 42 children aged 12 months to 13 years, 22 children received the dose of *VARILRIX* and 20 children received placebo. Similar percentages (respectively 41% and 45%) of children contracted varicella, but the risk of developing a moderate to severe form of the disease was eight times higher in the placebo group compared to the vaccinated group (relative risk. = 8.0, 95% CI 1.2-51.5, P: 0.003) (see section *4.4 Special warnings and precautions for use*).

5.2 Pharmacokinetic Properties

Evaluation of the pharmacokinetic properties is not required for vaccines.

5.3 Preclinical Safety Data

Not relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Powder: Anhydrous Lactose, Sorbitol, Mannitol, Amino acids

Solvent: Water for injectable preparations.

Neomycin sulphate is present as a residual from the manufacturing process.

6.2 Incompatibilities

VARILRIX should not be mixed with other vaccines in the same syringe.

6.3 Shelf-life

24 months.

The reconstituted vaccine can be kept for 90 minutes maximum at room temperature (25° C) or kept in a refrigerator (+2° to +8°C) for 8 hours maximum. If the reconstituted vaccine is not used within these periods of time, it should be discarded.

The expiry date is indicated on the label and packaging.

6.4 Special precautions for storage

VARILRIX should be kept in a refrigerator (between 2° C and 8° C).

For storage conditions after reconstitution of the medicinal product, see section *6.3 Shelf life*.

Keep out of reach of children.

6.5 Nature and contents of container

Box containing a single-dose vial of vaccine accompanied by a pre-filled syringe or an ampoule of solvent. The containers are of Type I neutral glass (European Pharmacopeia).

All presentations may not be marketed in India.

6.6 Special precautions for disposal and other handling

Small pH variations can cause the color of the reconstituted vaccine to vary from pale peach to pink without changing the quality of the vaccine.

Before administration, inspect the solvent and the reconstituted vaccine visually to detect any foreign particles and/or any change in the physical appearance prior to reconstitution or administration. In the event of either being observed, do not use the solvent or the reconstituted vaccine.

Instructions for reconstitution of the vaccine with the solvent presented in ampoules

VARILRIX should be reconstituted by adding the entire contents of the ampoule of solvent supplied to the vial of powder. ***T***he mixture should be well shaken until the powder is completely dissolved.

The vaccine should be used rapidly after reconstitution.

Withdraw the entire contents of the vial.

A new needle must be used to administer the vaccine.

Instructions for reconstitution of the vaccine with the solvent presented in a pre-filled syringe.

VARILRIX is reconstituted by adding the entire contents of the pre-filled syringe of solvent to the vial containing the powder.

To attach the needle to the syringe, please read the instructions in Figure 1 and 2 carefully. Note however that the syringe supplied with *VARILRIX* may differ slightly (without threading) from the syringe described in the drawing

In this case, the needle should not be screwed in for attachment to the syringe.

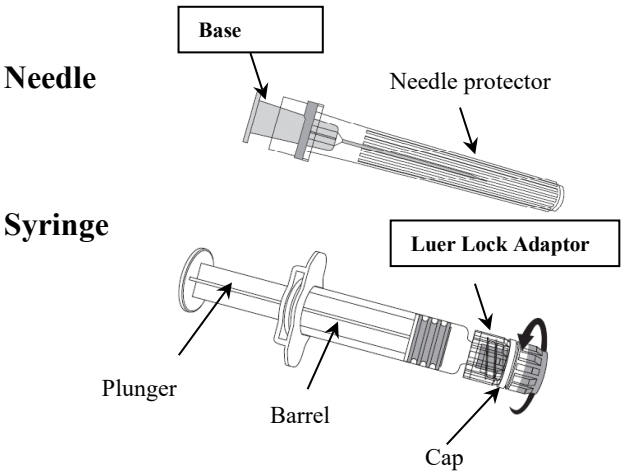

Figure 1

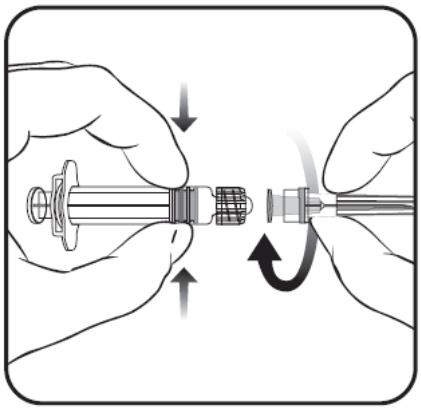

Figure 2

Always hold the syringe by the barrel, not the plunger or the Luer Lock Adaptor (LLA), and keep the needle in line with the syringe (see Figure 2). Failure to comply with this instruction could cause deformation of or leakage from the LLA.

During assembly of the syringe, if the LLA becomes detached, a new dose of vaccine must be used (new syringe and new vial).

1. Unscrew the syringe cap by turning it anticlockwise (see Figure 1).

Whether the LLA turns or not, please follow the steps below:

2. Attach the needle to the syringe by carefully placing the needle base in the LLA and rotating it one quarter turn clockwise until you feel it is locked (see Figure 2).

3. Remove the needle protector, can be a little difficult.

4. Add the solvent to the powder. The mixture should be well shaken until the powder is completely dissolved in the solvent.

The vaccine should be used promptly after the reconstitution.

5. Withdraw the entire contents of the vial.

6. A new needle should be used to administer the vaccine. Unscrew the needle from the syringe and attach the needle for injection by repeating step 2 above.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited,
Registered office
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

8. MARKETING AUTHORISATION NUMBER(S)

File no. :12-70/96-DC

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorization: 19th June 1998.

For further information please contact:
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