VARILRIX

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

VARILRIX Lyophilised virus vaccine. Powder for solution and injection.

2. QUALITATIVE AND QUANTITATIVE:

VARILRIX is a lyophilised preparation of the live attenuated OKa strain of the varicella-zoster virus, obtained by propagation of the virus in MRC_5 human diploid cell culture.

Each 0,5 ml of the reconstituted vaccine contains not less than 2000 plaque forming units (PFU) of the live attenuated varicella-zoster (OKa strain) virus.

Contains sugar (anhydrous lactose 32 mg/dose) and sugar alcohol (mannitol 8 mg/dose, sorbitol 6 mg/dose).

For full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM:

Powder for solution and injection.

Vaccine: Cream to yellowish or pinkish coloured cake or powder of lyophilised vaccine.

Diluent: Clear and colourless liquid.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Healthy subjects: VARILRIX is indicated for active immunisation against varicella of healthy infants (from the age of 9 months), children and adolescents.

High-risk patients and healthy close contacts: VARILRIX is also indicated for active immunisation against varicella of susceptible high-risk patients and their susceptible healthy close contacts.

Patients with acute leukaemia: Patients suffering from leukaemia have been recognised to be at special risk when they develop varicella and should therefore receive the vaccine if they have no history of the disease or are found to be seronegative.

When immunising patients in the acute phase of leukaemia: Maintenance chemotherapy should be withheld one week before and one week after immunisation. Patients under radiotherapy should normally not be immunised during the treatment phase.

Patients under immunosuppressive treatment: Patients under immunosuppressive treatment (including corticosteroid therapy) for malignant solid tumours or for serious chronic diseases (such as chronic renal failure, auto-immune diseases, collagen diseases, severe bronchial asthma) are predisposed to severe varicella.
Generally, patients are immunised when they are in complete haematological remission from the disease. It is advised that the total lymphocyte count should be at least 1 200/mm^3 or no other evidence of lack of cellular immune competence exists.

Patients with planned organ transplantation: If organ transplantation (e.g., kidney transplant) is being considered, immunisation should be carried out a few weeks before the administration of the immunosuppressive treatment.
Patients with chronic diseases: Other chronic diseases, such as metabolic and endocrine disorders, chronic pulmonary and cardiovascular diseases, mucoviscidosis and neuromuscular abnormalities may also predispose to severe varicella.
Healthy close contacts: Susceptible healthy close contacts should be immunised in order to reduce the risk of transmission of the 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.

Healthy Subjects:

- **Children 9 months up to and including 12 years of age:**

  Children from the age of 9 months up to and including 12 years of age should receive 2 doses of VARILRIX to ensure optimal protection against varicella.

  It is preferable to administer the second dose at least 6 weeks after the first dose but in no circumstances less than 4 weeks.

- **Adolescents and adults from 13 years of age and above:**

  From 13 years of age and above: 2 doses. It is preferable to administer the second dose at least 6 weeks after the first dose but in no circumstances less than 4 weeks.

High-risk patients:

In high-risk patients additional doses of vaccine might be required.

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.

Method of administration:

VARILRIX is to be injected subcutaneously (SC) or intramuscularly (IM) in the deltoid region or in the anterolateral area of the thigh.

VARILRIX should **not** be administered intradermally.

VARILRIX should be administered subcutaneously in subjects with bleeding disorders (e.g., thrombocytopenia or any coagulation disorder).

Note: VARILRIX must under no circumstances be administered intravenously.

Use and handling:

The diluent and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to reconstitution or administration. In the event of either being observed, do not use the diluent or the reconstituted vaccine.

VARILRIX must be reconstituted by adding the contents of the supplied container of diluent to the vial containing the powder. The mixture should be well shaken until the powder is completely dissolved in the diluent. Due to minor variations of its pH, the colour of the reconstituted vaccine may vary from clear peach to pink coloured solution.

Instructions for reconstitution of the vaccine with diluent presented in ampoules:

VARILRIX must be reconstituted by adding the entire contents of the supplied ampoule of diluent to the vial containing the powder. The mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used immediately.

Withdraw the entire contents of the vial.

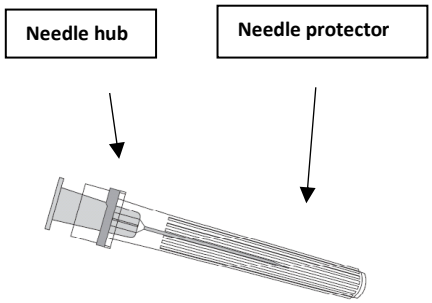
A new needle should be used to administer the vaccine. The administration needle should be for subcutaneous or intramuscular injection.

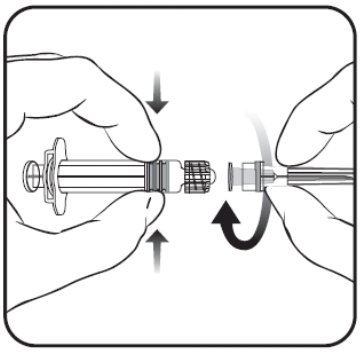
Instructions for reconstitution of the vaccine with diluent presented in pre-filled syringe:

VARILRIX must be reconstituted by adding the entire content of the pre-filled syringe of diluent to the vial containing the powder.

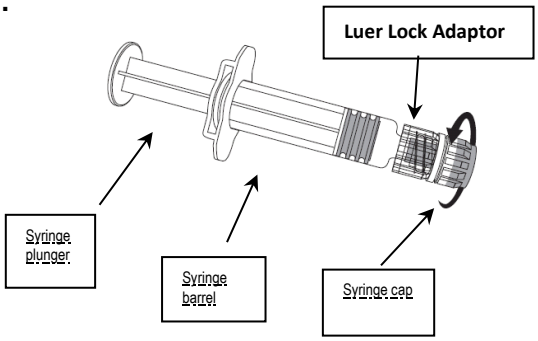
To attach the needle to the syringe, carefully read the instructions given with pictures 1 and 2. However, the syringe provided with VARILRIX might be slightly different than the syringe illustrated.

Needle:





Syringe:



Picture 1

Picture 2

Always hold the syringe by the barrel, not by the syringe plunger or the Luer Lock Adaptor (LLA) and maintain the needle in the axis of the syringe (as illustrated in picture 2). Failure to do this may cause the LLA to become distorted and leak.

During assembly of the syringe, if the LLA comes off, a new vaccine dose (new syringe and vial) should be used.

1. Unscrew the syringe cap by twisting it anticlockwise (as illustrated in picture 1).
2. Attach the needle to the syringe by gently connecting the needle hub into the LLA and rotate a quarter turn clockwise until you feel it lock (as illustrated in picture 2).

3. Remove the needle protector, which may be stiff.
4. Add the diluent to the powder. The mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used immediately.

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 injection needle by repeating step 2 above. The administration needle should be for subcutaneous or intramuscular injection.

4.3 Contraindications:

VARILRIX is contraindicated in subjects with severe humoral or cellular immunodeficiency such as:

- subjects with primary or acquired immunodeficiency states, with a total lymphocyte count less than 1 200 per mm^3
- subjects presenting other evidence of lack of cellular immune competence (e.g., subjects with leukaemia's, lymphomas, blood dyscrasias, clinically manifest HIV infection
- subjects receiving immunosuppressive therapy, including high dose corticosteroids (see section 4.4).

VARILRIX is contraindicated in subjects with known hypersensitivity to neomycin, or to any component of the vaccine. A history of contact dermatitis to neomycin is not contraindicated.

VARILRIX is contraindicated in pregnant women. Pregnancy should be avoided for one month after immunisation (see section 4.6).

In high-risk patients, VARILRIX should not be administered at the same time as other live attenuated vaccines. Inactivated vaccines may be administered in any temporal relationship to VARILRIX, given that no specific contra-indication has been established.

4.4 Special warnings and precautions for use:

The administration of VARILRIX should be postponed in patients suffering from acute severe febrile illness. In healthy subjects, the presence of minor infection, however, is not a contraindication for immunisation.

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.

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.

Limited protection against varicella may be obtained by vaccination up to 72 hours after exposure to natural disease.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

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 as compared to cases in unvaccinated individuals.

Transmission of the Oka vaccine virus has been shown to occur at a very low rate in seronegative contacts of vaccinees with rash. Transmission of the Oka vaccine from a vaccinee who does not develop a rash to seronegative contacts cannot be excluded.

It is advised that contact of vaccinees with persons who may be immunocompromised due to HIV infection or other immunodeficiency should be avoided for at least 14 days post immunisation.

There is limited data on the use of VARILRIX in immunocompromised subjects, therefore vaccination should be considered with caution and only when, in the opinion of the physician, the benefits outweigh the risks.

Immunocompromised subjects who have no contraindication for this vaccination (see section 4.3) may not respond as well as immunocompetent subjects, therefore some of these subjects

may acquire varicella despite appropriate vaccine administration. Immunocompromised subjects should be monitored carefully for signs of varicella.

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

In high-risk patients VARILRIX should not be administered at the same time as other live attenuated vaccines.

VARILRIX must not be administered intravascularly or intradermally.

Appropriate medical treatment should always be readily available including adrenaline in case of rare anaphylactic reactions following administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunisation.

It must be expected that the reactogenicity following co-administration of VARILRIX and more reactogenic vaccines will be determined by the reactions of the latter.

Excipient Warnings:

VARILRIX contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not be given VARILRIX (see section 6.1).

VARILRIX contains traces of neomycin. VARILRIX should not be used in patients with a known hypersensitivity to this antibiotic.

4.5 Interactions with other medicines and other forms of interaction:

If tuberculin testing has to be done 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.

In subjects who have received immune globulin or a blood transfusion, immunisation should be delayed for at least three months because of likelihood of vaccine failure 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.

Healthy subjects:

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

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.

High-risk patients:

VARILRIX should not be administered at the same time as other live attenuated vaccines. Inactivated vaccines may be administered in any temporal relationship to VARILRIX, given that no specific contraindication has been established. However, different injectable vaccines should always be administered at different injection sites (see section 4.3).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

VARILRIX is contraindicated during pregnancy. Pregnant women must not be vaccinated with VARILRIX. Pregnancy should be avoided for one month after immunisation (see section 4.3).

Women who intend to become pregnant should be advised to delay pregnancy.

Adequate human data on the use of VARILRIX during pregnancy are not available and animal studies on reproductive toxicity have not been conducted.

Breastfeeding:

Administration of VARILRIX is not advised during breastfeeding.

Fertility:

No data available.

4.7 Effects on ability to drive and use machines:

It would not be expected that vaccination would affect the ability to drive or operate machinery.

4.8 Undesirable effects:

Clinical trial data:

Healthy subjects:

More than 7900 individuals have participated in clinical trials evaluating the reactogenicity profile of the vaccine administered subcutaneously either alone or concomitantly with other vaccines.

The safety profile presented below is based on a total of 5 369 doses of VARILRIX administered alone to children, adolescents and adults.

Frequencies are reported as follows:

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, including isolated reports.

System organ class	**Frequency**	**Adverse reactions**
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 ≥ 37,5 C or rectal temperature ≥ 38,0 C)*
	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 in children under 13 years of age.

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

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

In a clinical trial, 328 children aged 11 to 21 months received GSK's combined measles, mumps, rubella and varicella vaccine (containing the same varicella strain as VARILRIX) either by subcutaneous or intramuscular route. A comparable safety profile was observed for both administration routes.

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 data:

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

Infections and infestations: herpes zoster

Blood and lymphatic disorders: thrombocytopenia

Immune system disorders: hypersensitivity, anaphylactic reactions

Nervous system disorders: encephalitis, cerebrovascular accident, cerebellitis, cerebellitis like symptoms (including transient gait disturbance and transient ataxia), convulsions

Vascular disorders: vasculitis (including Henoch Schonlein purpura and Kawasaki syndrome)

Skin and subcutaneous tissue disorders: erythema multiforme**.**

Reporting of suspected adverse events:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 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. See section 4.8. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 30.2 Biologicals, Antigens

VARILRIX produces an attenuated clinically inapparent varicella infection in susceptible subjects. The presence of antibodies is accepted to be an indication of protection.
The efficacy of GlaxoSmithKline (GSK)'s Oka varicella vaccines in preventing confirmed varicella disease (by Polymerase Chain Reaction (PCR) or exposure to varicella case) has been evaluated in a large active controlled multicountry clinical trial in which children aged 12-22 months received one dose of VARILRIX or two doses of combined measles, mumps, rubella and varicella (Oka) vaccine. Vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella was demonstrated after a primary follow-up period of 2 years (median duration 3,2 years). Persistent efficacy was observed in the same study during the long-term follow-up period of 6 years (median duration 6,4 years) and 10 years (median duration 9,8 years). The data are presented in the Table below.

Group	Timing	Efficacy against confirmed varicella of any severity	Efficacy against moderate or severe confirmed varicella
VARILRIX (1 dose)	Year 2	65,4 % (97,5 % CI: 57,2;72,1)	90,7 % (97,5 % CI: 85,9;93,9)

N = 2 487	Year 6[(1)]	67,0 % (95 % CI: 61,8;71,4)	90,3 % (95 % CI: 86,9;92,8)
	Year 10[(1)]	67,2 % (95% CI: 62,3;71,5)	89,5 % (95% CI: 86,1;92.1)
Combined measles, mumps, rubella and varicella (Oka) vaccine (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)
	Year 10[(1)]	95,4 % (95 % CI: 94,0;96,4)	99,1 % (95 % CI: 97,9;99,6)

N = number of subjects enrolled and vaccinated

(1) descriptive analysis

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 hospitalisations and ambulatory visits among children were respectively 81 % and 87 % overall.

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

Immune response after intramuscular administration:

The immunogenicity of VARILRIX administered intramuscularly is based on a comparative study where 283 healthy children aged 11 to 21 months received GSK's combined measles, mumps, rubella and varicella vaccine (containing the same varicella strain as VARILRIX) either by subcutaneous or intramuscular route. Comparable immunogenicity was demonstrated for both administration routes.

5.2 Pharmacokinetic properties:

Evaluation of pharmacokinetic properties is not required for vaccines.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Powder: amino acids, lactose, mannitol and sorbitol.

Diluent: water for injection.

Residues: neomycin sulphate.

6.2. Incompatibilities:

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

6.3 Shelf life:

24 months

6.4 Special precautions for storage:

Store in refrigerator between +2 °C and +8 °C. Protect from light.

Discard any unused portion.

Keep all medicines out of reach of children.

6.5 Nature and contents of container:

The vaccine is presented in a 3 ml clear glass vial with a rubber stopper.

The diluent is presented in a clear glass ampoule or a pre-filled syringe with 2 needles.

6.6 Special precautions for disposal and other handling:

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

Appearance of Reconstituted vaccine: Clear peach to pink coloured solution, free from visible particles.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

32/30.1/0468

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Date of registration: 11 January 2000

10. DATE OF REVISION OF TEXT:

21 June 2021

GDS-15

Namibia: Reg No 04/30.1/0879 NS1

Manufacturing details

Lyophilised powder in vials:

Corixa Corporation dba GlaxoSmithKline Vaccines

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Lyophilised powder in vials:

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