

Varilrix
Varicella vaccine
Powder and solvent for solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

VARILRIX is a lyophilised preparation of the live attenuated Oka strain of varicella-zoster virus, obtained by propagation of the virus in MRC-5 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 attenuated varicella-zoster virus.

The powder is slightly cream to yellowish or pinkish.
The solvent is clear and colourless.

CLINICAL INFORMATION

Indications

Healthy subjects

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

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 receive 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 tumour 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 per mm³ 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 virus to high-risk patients. These include parents and siblings of high-risk patients, medical, paramedical personnel and other people who are in close contact with varicella patients or high-risk patients.

Dosage and Administration

0.5 ml of reconstituted vaccine contains one immunising dose.

Posology

Healthy subjects

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

Children from the age of 12 months up to and including 12 years of age should receive 2 doses of VARILRIX to ensure optimal protection against varicella (*see "Pharmacodynamics"*).

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

[*Note: Applicable official recommendations may vary regarding the interval between doses and the need for one or two doses of varicella-containing vaccines in children aged 12 months to 12 years*].

- **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

The same schedule described for healthy subjects should be applied for high-risk patients. In these patients, periodic measurement of varicella antibodies after vaccination may be indicated in order to identify those who may benefit from re-vaccination.

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 for subcutaneous administration in the deltoid region or in the anterolateral area of the thigh.

For instructions on reconstitution of the medicinal product before administration, see “*Instructions for Use/Handling*”.

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 immunisation.

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 mm³;
- subjects presenting other evidence of lack of cellular immune competence (e.g. subjects with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infection);
- subjects receiving immunosuppressive therapy including high dose of corticosteroids.

See also “*Warnings and Precautions*”.

VARILRIX is contraindicated in subjects with known hypersensitivity to neomycin, or to any other component of the vaccine, or to any other varicella vaccine.

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

VARILRIX is contraindicated in pregnant women. Pregnancy should be avoided for one month after vaccination (see “*Pregnancy and Lactation*”).

Warnings and Precautions

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. 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.

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.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after 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 "Contraindications"*) 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.

VARILRIX must not be administered intravascularly or intradermally.

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

Serological studies of efficacy and post-marketing experience indicate that the vaccine does not completely protect all individuals from naturally-acquired varicella and cannot be expected to provide maximal protection against infection with varicella-zoster virus until about six weeks after the second dose.

Administration of VARILRIX to subjects who are in the incubation period of the infection cannot be expected to protect against clinically manifest varicella or to modify the course of the disease.

The rash produced during the naturally-acquired primary infection with varicella-zoster may be more severe in those with existing severe skin damage, including severe eczematous conditions. It is not known if there is an increased risk of vaccine-associated skin lesions in such persons, but this possibility should be taken into consideration before vaccination.

In healthy contacts of vaccinees, seroconversion has sometimes occurred in the absence of any clinical manifestations of infection. Clinically apparent infections due to transmission of the vaccine viral strain have been associated with few skin lesions and minimal systemic upset.

However, contact with the following groups must be avoided if the vaccinee develops a cutaneous rash thought likely to be vaccine-related (especially vesicular or papulovesicular) within four to six weeks of the first or second dose and until this rash has completely disappeared (*see also sections on Pregnancy and Lactation and Pharmacological Properties*):

- varicella-susceptible pregnant women and
- individuals at high risk of severe varicella, such as those with primary and acquired immunodeficiency states. These include individuals with leukaemia, lymphomas, blood dyscrasias, clinically manifest HIV infections, and patients who are receiving immunosuppressive therapy, including high dose corticosteroids.

In the absence of a rash in the vaccinee, the risk of transmission of the vaccine viral strain to contacts in the above groups appears to be extremely small. Nevertheless, vaccinees (e.g. healthcare workers) who are very likely to come into contact with persons in the above groups should preferably avoid any such contact during the period between vaccinations and for 4-6 weeks after the second dose. If this is not feasible, then vaccinees should be vigilant regarding the reporting of any skin rash during this period, and should take steps as above if a rash is discovered.

Interactions

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 globulins or a blood transfusion, immunisation should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired varicella antibodies.

Aspirin and systemic salicylates should not be given to children under the age of 16, except under medical supervision, because of the risk of Reye's syndrome. Reye's syndrome has been reported in children treated with aspirin 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.

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.

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. Different injectable vaccines should always be administered at different injection sites.

Pregnancy and Lactation

Fertility

No data available.

Pregnancy

VARILRIX contains a live attenuated varicella-zoster virus. Pregnant women must not be vaccinated with VARILRIX. Pregnancy should be avoided for one month after vaccination. 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.

Varicella-zoster virus may cause severe clinical disease in pregnant individuals and may adversely affect the foetus and/or result in perinatal varicella, depending on the gestational stage when the infection occurs. Because the possible effects of infection with the vaccine viral strain on the mother and on the foetus are unknown, VARILRIX must not be administered to pregnant women.

Lactation

It is not known whether VARILRIX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VARILRIX is administered to a nursing woman.

Adverse Reactions

Clinical trial data

Healthy subjects

More than 7,900 individuals have participated in clinical trials evaluating the reactogenicity profile of the vaccine administered alone or concomitantly with other vaccines.

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

Frequencies are reported as:

Very common ($\geq 1/10$) /

Common ($\geq 1/100$ to $< 1/10$) /

Uncommon ($\geq 1/1,000$ to $< 1/100$) /

Rare ($\geq 1/10,000$ to $< 1/1,000$) /

Very rare ($< 1/10,000$)

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 $\geq 37.5^{\circ}\text{C}$ 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

* 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 the first dose.

No difference was 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

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

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Rare	Herpes zoster
Blood and lymphatic system disorders	Rare	Thrombocytopenia
Immune system disorders	Rare	Hypersensitivity, anaphylactic reactions
Nervous system disorders	Rare	Encephalitis, cerebrovascular accident, cerebellitis, cerebellitis-like symptoms (including transient gait disturbance and transient ataxia), convulsions
Vascular disorders	Rare	Vasculitis (including Henoch-Schonlein purpura and Kawasaki syndrome)
Skin and subcutaneous tissue disorders	Rare	Erythema multiforme

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

Mechanism of action

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

Pharmacodynamics

ATC code J07B K01

The Oka strain virus contained in VARILRIX was initially obtained from a child with natural varicella; the virus was then attenuated through sequential passage in tissue culture.

Natural infection induces a cellular and humoral immune response to the varicella-zoster virus, which can be rapidly detected following infection. IgG, IgM and IgA directed against viral proteins usually appear at the same time that a cellular immune response can be demonstrated, making the relative contribution of humoral and cellular immunity to disease progression difficult to ascertain. Vaccination has been shown to induce both humoral and cell-mediated types of immunity.

In clinical trials, the immune response to vaccination was routinely measured using an immunofluorescence assay. Antibody titres of $\geq 1:4$ (the detection level of the test) were considered as positive.

Efficacy and effectiveness

The efficacy of GlaxoSmithKline (GSK)'s monovalent Oka (VARILRIX) and Priorix-Tetra vaccines in preventing varicella disease has been evaluated in a large randomized multicountry clinical trial, which included GSK combined measles-mumps-rubella vaccine, Priorix as control. The trial has been conducted in European countries where no routine varicella vaccination is implemented.

Children aged 12-22 months received two doses of combined measles, mumps, rubella and varicella vaccine six weeks apart or one dose of VARILRIX.

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 periods 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) 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)
	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 hospitalizations 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.

In clinical trials that enrolled 211 adolescents and 213 adults, all vaccinees had detectable levels of antibodies in blood samples taken six weeks after the second vaccine dose. Virtually all (98.7%) of the 1637 children tested had detectable antibodies six weeks after immunisation with one dose of vaccine.

Virtually all ($\geq 98.7\%$) children aged 9 months to 12 years tested had antibody levels ≥ 4 (dil-1) six weeks after immunisation with one dose of VARILRIX.

All of 659 children aged 9 months to 6 years, who received a second dose of VARILRIX or received VARILRIX after a first dose of another varicella vaccine, had antibody levels ≥ 4 (dil-1) at 6-18 weeks following vaccination. There was a large increase in GMT (up to 13-fold) between post-dose 1 and post-dose 2.

However, the safety and immunogenicity of a second dose of VARILRIX in adolescents (≥ 13 years) and adults primed with another varicella-containing vaccine has not been specifically studied in clinical trials.

In a follow-up study over 2 years in 159 vaccinated adult health care workers, 2 out of 72 (3%) vaccinees reporting contacts with wild-type chickenpox experienced mild breakthrough disease. Approximately one-third of the vaccinees showed an increase in antibody titre over the follow-up period, indicative of contact with the virus, without clinical evidence of varicella infection.

The percentage of vaccinees who will later experience herpes zoster due to reactivation of the Oka strain virus is currently unknown. However, the risk of zoster after vaccination is currently thought to be much lower than would be expected after wild-type virus infection, due to attenuation of the vaccine strain.

Clinical Studies

See section "*Pharmacodynamics*".

PHARMACEUTICAL PARTICULARS

List of Excipients

Excipients of the vaccine are: amino acids, lactose, mannitol, sorbitol.
Solvent is water for injections.

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

Shelf Life

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).

Special Precautions for Storage

The lyophilised vaccine should be stored in a refrigerator (2°C-8°C) and protected from light. The solvent can be stored in the refrigerator or at ambient temperature. The lyophilised vaccine is not affected by freezing.

When supplies of VARILRIX are distributed from a central cold store, it is necessary to arrange transport under refrigerator conditions.

After reconstitution, it is recommended that the vaccine be injected as soon as possible. (see *Shelf-Life*).

The storage conditions are detailed on the packaging.

Nature and Contents of Container

VARILRIX is presented in a glass vial.
The sterile solvent is presented in ampoules and pre-filled syringes.
Not all presentations are available in every country.

Incompatibilities

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

Instructions for Use/Handling

Due to minor variations of its pH, the colour of the reconstituted vaccine may vary from clear peach to pink coloured solution.

The solvent 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 solvent or the reconstituted vaccine.

Instructions for reconstitution of the vaccine with solvent presented in ampoules

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

After reconstitution, the vaccine should be used promptly.

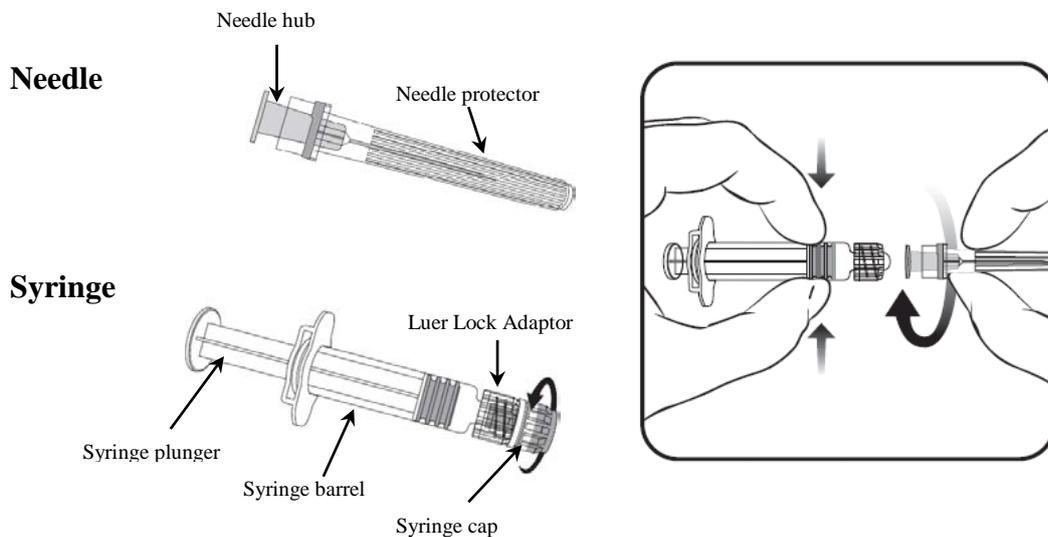
Withdraw the entire contents of the vial.

A new needle should be used to administer the vaccine.

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

VARILRIX must be reconstituted by adding the entire content of the pre-filled syringe of solvent 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.



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

After reconstitution, the vaccine should be used promptly.

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.

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

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Manufacturer

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