
VARILRIX

Versión GDSv19-IPIv20

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 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 attenuated varicella-zoster virus.

The powder is slightly cream to yellowish or pinkish.

The solvent is clear and colourless.

Clinical Information

Indications

Varilrix is indicated for active immunisation against varicella:

- In healthy individuals from the age of 9 months (see *Pharmacodynamic effects*);
- For post-exposure prophylaxis if administered to healthy, susceptible individuals exposed to varicella within 72 hours of contact (see *Warnings and Precautions* and *Pharmacodynamic effects*);
- In individuals at high risk of severe varicella (see *Contraindications, Warnings and Precautions* and *Pharmacodynamic effects*).

Vaccination of susceptible healthy close contacts of individuals at risk of severe varicella is recommended, in order to reduce the risk of transmission of wild-type virus to these individuals. Close contacts include parents and siblings of high-risk individuals, and medical and paramedical personnel.

As there is only limited data from clinical trials available for Varilrix (+4°C formulation) in individuals at high risk of severe varicella, should vaccination be considered, it is advised that:

- maintenance chemotherapy should be withheld one week before and one week after immunisation of patients in the acute phase of leukaemia. Patients under radiotherapy should normally not be vaccinated during the treatment phase. Generally patients are immunised when they are in complete haematological remission from their disease.
- the total lymphocyte count should be at least $1,200 \text{ per mm}^3$ or no other evidence of lack of cellular immune competence exists.
- vaccination should be carried out a few weeks before the administration of the immunosuppressive treatment for patients undergoing organ transplantation (e.g. kidney transplant).

Dosage and Administration

0.5 mL of reconstituted vaccine contains one immunising dose.

Posology

The immunisation schedules for Varilrix should be based on official recommendations.

Healthy individuals

Children from the age of 9 months as well as adolescents and adults receive two doses of Varilrix to ensure optimal protection against varicella (see *Pharmacodynamic effects*). The second dose should generally be given at least 6 weeks after the first dose. Under no circumstances should the interval between the doses be less than 4 weeks.

Post-exposure prophylaxis susceptible individuals exposed to varicella should receive one dose of Varilrix within 72 hours of contact.

Individuals at High Risk of Severe Varicella

The same schedule described for healthy individuals should be applied for individuals at high risk of severe varicella (see *Pharmacodynamic effects*).

In these individuals, periodic measurement of varicella antibodies after vaccination may be indicated in order to identify those who may benefit from re-vaccination. In individuals at high risk of severe varicella additional doses of vaccine might be required. Under no circumstances should the interval between the doses be less than 4 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.

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 be administered subcutaneously in individuals with bleeding disorders (e.g. thrombocytopenia or any coagulation disorder).

For instructions on reconstitution of the medicinal product before administration see *Use and Handling*.

Contraindications

Varilrix is contraindicated in individuals with severe humoral or cellular immunodeficiency such as:

- patients with primary or acquired immunodeficiency states with a total lymphocyte count less than $1,200 \text{ per mm}^3$;
- patients presenting other evidence of lack of cellular immune competence (e.g. patients with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infection);
- patients on current or recent immunosuppressive therapy (includes high doses of corticosteroids but not topical or low-dose parenteral corticosteroids). (See also *Warnings and Precautions*).

Varilrix is contraindicated in individuals with known hypersensitivity to neomycin or to any other component of the vaccine (see *Qualitative and Quantitative Composition and List of Excipients*). A history of contact dermatitis to neomycin is not a contraindication.

Varilrix is contraindicated in individuals 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*).

Warnings and Precautions

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

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 (see *Pharmacodynamic effects*).

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

The mild nature of the rash in the healthy contacts indicates that the virus remains attenuated after passage through human hosts.

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.

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

Immunocompromised patients who have no contraindication for this vaccination (see *Contraindications*) may not respond as well as immunocompetent individuals, therefore some of these individuals may acquire varicella despite appropriate vaccine administration. Immunocompromised individuals should be monitored carefully for signs of varicella.

Due to the potential risk of decreased vaccine response and/or disseminated disease, consideration should be given to the time interval between Varilrix vaccination and immunosuppressive therapy (see *Contraindications*).

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

Varilrix must not be administered intravascularly or intradermally.

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 individuals who have received immune globulins or a blood transfusion, immunisation should be delayed for at least 3 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.

Healthy Individuals

Clinical studies with varicella-containing vaccines support concomitant administration of Varilrix with any of the following monovalent or combination vaccines: measles-mumps-rubella vaccine (MMR), diphtheria-tetanus-acellular pertussis vaccine (DTPa), reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), hexavalent vaccine (DTPa-HBV-IPV/Hib), hepatitis A vaccine (HAV), meningococcal serogroup B vaccine (Bexsero), meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W and Y conjugate vaccine (MenACWY) and pneumococcal conjugate vaccine (PCV).

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.

Individuals at High Risk of Severe Varicella

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

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.

Lactation

There are no data regarding use in breast-feeding women.

Effects on Ability to Drive and Use Machines

No studies on the effects of Varilrix on the ability to drive and use machines have been performed.

Adverse Reactions

Clinical Trial Data

Healthy Subjects

More than 7,900 subjects 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:

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.

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.

Individuals at High Risk of Severe Varicella

There are only very limited data from clinical trials available in subjects 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

The following additional adverse reactions have been identified in rare occasions during post-marketing surveillance. Because they are reported voluntarily from a population of unknown size, a true estimate of frequency cannot be provided:

System Organ Class	Adverse reactions
Infections and infestations	herpes zoster
Blood and lymphatic system disorders	thrombocytopenia
Immune system disorders	hypersensitivity, anaphylactic reactions
Nervous system disorders	encephalitis, cerebrovascular accident, 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

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

Pharmacodynamics

ATC code

Pharmaco-therapeutic group: Viral vaccines, ATC code J07BK01.

Mechanism of action

Varilrix produces an attenuated clinically inapparent varicella infection in susceptible individuals.

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

Pharmacodynamic effects

Efficacy and effectiveness

Healthy subjects

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 multi-country clinical trial, which included the combined measles-mumps-rubella vaccine (Priorix) as active control.

Children aged 12-22 months received one dose of Varilrix or two doses of the combined measles, mumps, rubella and varicella (Oka) vaccine (Priorix-Tetra). Vaccine efficacy against confirmed varicella of any severity and against moderate

or severe confirmed varicella was observed 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
Monovalent varicella (Oka) vaccine (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 (Priorix-Tetra) 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

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).

There are insufficient data to assess the rate of protection against complications of chickenpox such as encephalitis, hepatitis or pneumonia.

Effectiveness data, deriving from observation in different contexts (epidemic onset, case-control studies, observational studies, databases, models) suggest a higher level of protection and a decrease in the occurrence of cases of chickenpox following two doses of vaccine compared to a single dose.

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

Post-Exposure Prophylaxis

Published data on the prevention of varicella following exposure to the varicella virus are limited.

In a randomised, double-blind, placebo-controlled study including 42 children aged between 12 months and 13 years, 22 children received one dose of Varilrix and 20 children received one dose of placebo within 3 days after exposure. Similar percentages (41% and 45%, respectively) of children contracted varicella, but the risk of developing a moderate to severe form of the disease was 8 times higher in the placebo group compared with the vaccinated group (relative risk = 8.0; 95% CI: 1.2; 51.5; P=0.003).

In a controlled study including 33 children aged between 12 months and 12 years, 15 received varicella vaccine (13 subjects received Varilrix and 2 subjects received another Oka strain varicella vaccine) up to 5 days after exposure and 18 subjects were not vaccinated. When considering the 12 children vaccinated within 3 days after exposure, vaccine effectiveness was 44% (95% CI: -1; 69) in preventing any disease and 77% (95% CI: 14; 94) in preventing moderate or severe disease.

In a prospective cohort study (with historic attack rates as control), 67 children, adolescents or adults received varicella vaccine (55 subjects received Varilrix and 12 subjects received another Oka strain varicella vaccine) within 5 days after exposure. Vaccine effectiveness was 62.3% (95% CI: 47.8; 74.9) in preventing any type of disease and 79.4% (95% CI: 66.4; 88.9) in preventing moderate and severe disease.

Individuals at High Risk of Severe Varicella

Patients suffering from leukaemia, patients under immunosuppressive treatment (including corticosteroid therapy) for malignant solid tumour, for serious chronic diseases (such as chronic renal failure, auto-immune diseases, collagen diseases, severe bronchial asthma) or following organ transplantation, are predisposed to severe natural varicella. Vaccination with the Oka-strain has been shown to reduce the complications of varicella in these patients.

Immune Response After Subcutaneous Administration

Healthy Subjects

In children aged 11 months to 21 months the seroconversion rate, when measured by Enzyme-linked Immunosorbent Assay (ELISA) 6 weeks after vaccination, was 89.6% after one vaccine dose and 100% after the second vaccine dose.

In children aged 9 months to 12 years, the overall seroconversion rate when measured by Immunofluorescence Assay (IFA) 6 weeks after vaccination was >98% after one vaccine 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 of geometric mean titres 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.

Individuals at High Risk of Severe Varicella

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

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.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See Pharmacodynamic effects.

Non-Clinical Information

Non-clinical data reveal no special hazard for humans based on general safety tests performed in animals.

Pharmaceutical Information

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 is indicated on the 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).

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, transport must be done under refrigerator conditions especially in hot climates.

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.

Incompatibilities

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

Use and Handling

Due to minor variations of its pH, the colour of the reconstituted vaccine may vary from clear peach to pink coloured solution. Presence of translucent product-related particulates may be observed after reconstitution. This is normal and does not impair the performance of the vaccine.

The solvent and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of 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 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.

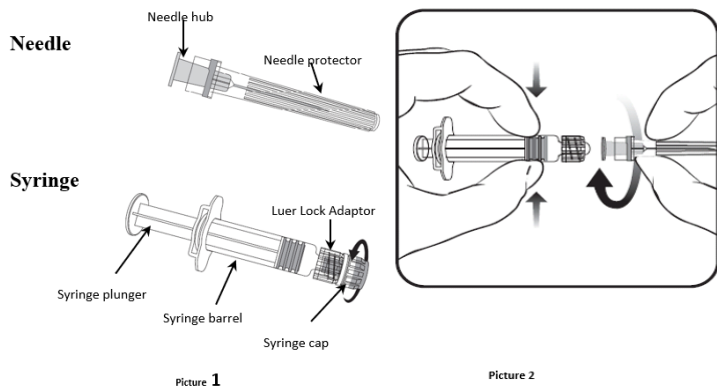
Withdraw the entire contents of the vial.

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 contents 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 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 solvent to the powder. The mixture should be well shaken until the powder is completely dissolved in the solvent.
5. After reconstitution, the vaccine should be used promptly.
6. Withdraw the entire contents of the vial.
7. 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.

Not all presentations are available in every country.

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