

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

VARILRIX

2. 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.

Each dose of the reconstituted vaccine contains not less than 103.3 plaque-forming units (PFU) of the attenuated varicella-zoster virus.

3. PHARMACEUTICAL form

The powder is slightly cream to yellowish or pinkish.

The solvent is clear and colourless.

4. Clinical particulars

4.1 Therapeutic indications

Healthy subjects

Varilrix is indicated for active immunisation against varicella of healthy subjects from the age of 9 months onwards.

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

Patients 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.

There is only limited data from clinical trials available for Varilrix in patients 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 the disease.
- the total lymphocyte count should be at least 1,200 per mm³ 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).

4.2 Posology and method of administration

0.5 ml of reconstituted vaccine contains one immunising dose.

Posology

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.

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 9 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

4.3 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 contra-indication 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.

Varilrix is contraindicated in subjects with known hypersensitivity to neomycin or to any other component of the vaccine. A history of contact dermatitis to neomycin is not a contraindication.

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

4.4 Special warnings and precautions for use

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

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.

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 vaccine 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 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.

4.5 Interaction with other medicinal products 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 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.

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. 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.

4.6 Pregnancy and lactation

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

4.7 Undesirable effects

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	

* 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

4.8 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Varilrix produces an attenuated clinically inapparent varicella infection in susceptible subjects. The presence of antibodies is accepted to be an indication of protection.

Efficacy and effectiveness

The efficacy of GlaxoSmithKline'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 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, casecontrol 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.

Immune response

Healthy subjects

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

In 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 GMT increase).

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

In clinical trials, the majority of vaccinated subjects who were subsequently exposed to wildtype 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.

High-risk patients

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

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

Transmission of the Oka vaccine virus as shown by virus isolation and identification has been demonstrated in four cases in siblings of immuno-compromised vaccinees who had a vesicular eruption. Whenever those siblings of immuno-compromised vaccinees developed themselves a post-exposure rash, it was always very mild.

6. PHARMACEUTICAL PARTICULARS

6.1 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.

6.2 Incompatibilities

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

6.3 Shelf life

24 months

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).

6.4 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, 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.

The storage conditions are detailed on the packaging.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Varilrix is presented in a glass vial.

The sterile solvent is presented in ampoules and pre-filled syringes.

6.6 Special precautions for disposal and other 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.

7. APPLICANT/SUPPLIER

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