Varilrix

Summary of Product Characteristics Updated 19-Sep-2017 | GlaxoSmithKline UK

1. Name of the medicinal product

Varilrix 10 $^{3.3}$ PFU/0.5ml**,** powder and solvent for solution for injection.

2. Qualitative and quantitative composition

One dose (0.5 ml) contains:

Live attenuated varicella-zoster (Oka strain) virus* $10^{3.3}$ plaque forming units (PFU)

*propagated in MRC5 human diploid cells

For excipients, see 6.1.

3. Pharmaceutical form

Powder and solvent for solution for injection.

Clear peach to pink coloured solution.

4. Clinical particulars

4.1 Therapeutic indications

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

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.

4.2 Posology and method of administration

Posology

Children 9 months up to and including 12 years

Two doses (each of 0.5 ml of reconstituted vaccine) should be given to ensure optimal protection against varicella (see section 5.1).

- Children from 9 to 12 months of age

The second dose should be given after a minimum interval of 3 months.

- Children from 12 months to 12 years of age

The second dose should be given after an interval of at least 6 weeks but in no circumstances less than 4 weeks.

Varilrix should not be administered to children aged less than 9 months.

Adolescents and adults from 13 years of age and above

Two doses (each of 0.5 ml of reconstituted vaccine). It is preferable to administer the second dose at least 6 weeks after the first dose but in no circumstances less than 4 weeks.

Elderly

There are no data on immune responses to Varilrix in the elderly.

Interchangeability:

A single dose of Varilrix may be administered after a first dose of another varicella containing vaccine (see section 5.1).

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.

Varilrix should not be administered intravascularly or intradermally.

Varilrix must not be mixed with any other medicinal product in the same syringe (see also sections 4.5 and 6.2). For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Varilrix is contra-indicated in subjects who have a history of hypersensitivity to neomycin, or to any of the excipients in the vaccine, or to any other varicella vaccine.

A second dose of Varilrix is contra-indicated in subjects who have had a hypersensitivity reaction following the first

dose.

Varilrix is contra-indicated during pregnancy and breast-feeding (see also sections 4.4 and 4.6).

Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

Varilrix must not be administered to subjects with primary or acquired immunodeficiency states with a total lymphocyte count less than 1,200 per mm^3 or presenting other evidence of lack of cellular immune competence, such as subjects with leukaemias, lymphomas, blood dyscrasias, clinically manifest HIV infection, or patients receiving immunosuppressive therapy (including high dose corticosteroids).

Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinemia and AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25%; children between 12-35 months: CD4+ < 20%; children between 36-59 months: CD4+ < 15% (see section 4.4).

Administration of Varilrix must be postponed in subjects suffering from acute, severe febrile illness. In healthy subjects the presence of a minor infection, however, is not a contraindication.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

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.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents 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.

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 (see section 5.1).

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 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.

Transmission of the vaccine viral strain

Transmission of vaccine viral strain has been shown to occur from healthy vaccinees to healthy contacts, to pregnant contacts and to immunosuppressed contacts. However, transmission to any of these groups occurs rarely or very rarely.

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 4.6 and 5.1).

- 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 leukaemias, 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.

Healthy individuals may be vaccinated if they are close contacts of persons who are at high risk of severe varicella infection (see sections 4.1 and 4.2). In these circumstances, continued contact between the vaccinee and the person at risk may be unavoidable. Therefore, the risk of transmission of the attenuated vaccine viral strain from the vaccinee should be weighed against the potential for acquisition of wild-type varicella-zoster by the at-risk person.

The Oka vaccine viral strain has recently been shown to be sensitive to acyclovir.

Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (e.g. asymptomatic HIV subjects, IgG subclass deficiencies, congenital neutropenia,chronic granulomatous disease, and complement deficiency diseases).

Immunocompromised patients who have no contraindication for this vaccination (see section 4.3) may not respond as well as immunocompetent subjects, therefore some of these patients may acquire varicella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of varicella.

Patients with rare hereditary problems of fructose intolerance should not be vaccinated with VARILRIX as it contains sorbitol**.**

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, vaccination should be delayed for at least three months because of the likelihood of vaccine failure due to passively acquired antibody to the varicella-zoster virus.

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. However, there is no evidence to suggest that vaccination with Varilrix should be contraindicated for older age-groups who need to take aspirin.

In a study in which Varilrix was administered to toddlers at the same time as, but at a different site to, a combined measles, mumps and rubella vaccine, there was no evidence of significant immune interference between the live viral antigens.

If a measles containing vaccine is not given at the same time as Varilrix, it is recommended that an interval of at least one month between vaccinations is respected, since it is recognised that measles vaccination may cause short-term suppression of the cell-mediated response.

If it is considered necessary to administer another live vaccine at the same time as Varilrix, the vaccines must be given as separate injections and at different body sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnant women should not be vaccinated with Varilrix.

However, fetal damage has not been documented when varicella vaccines have been given to pregnant women.

Pregnancy should be avoided for 1 month following vaccination. Women who intend to become pregnant should be advised to delay.

Breast-feeding

The infants of seronegative women would not have acquired transplacental antibody to varicella-zoster virus. Therefore, due to the theoretical risk of transmission of the vaccine viral strain from mother to infant, women should not be vaccinated while breastfeeding.

Fertility

No fertility data are 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 trials in 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 5369 doses of Varilrix administered alone to children, adolescents and adults.

The most common adverse reactions observed after vaccine administration were injection site pain (23.8%), redness (19.9%) and swelling (12.1%).

Frequencies are reported as:

Very common:	≥1/10
Common:	≥1/100 and <1/10
Uncommon:	≥1/1,000 to <1/100
Rare:	≥1/10,000 and <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 ≥ 37.5℃ or rectal temperature ≥ 38.0℃)*
	Uncommon	fever (oral/axillary temperature > 39.0℃ or rectal temperature > 39.5℃), fatigue, malaise

* Swelling at the injection site and fever were very commonly reported 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 differences were seen in the reactogenicity profile between initially seropositive and initially seronegative subjects.

Post-marketing surveillance

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

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

Transmission of the vaccine virus from healthy vaccinees to healthy contacts has been shown to occur very rarely.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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 other cases, no associated adverse events were reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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.

Efficacy and effectiveness

The efficacy of GlaxoSmithKline (GSK)'s monovalent Oka/RIT (Varilrix) and Priorix-Tetra vaccines in preventing varicella disease has been evaluated in a large randomised 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 observed after a primary follow-up period of 2 years (median duration 3.2 years) and after an extended follow-up period of 6 years (median duration 6.4 years) 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)
Combined measles, mumps, rubella and varicella (Oka/RIT) 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)

N = number of subjects enrolled and vaccinated

(1) descriptive analysis

In a study in Finland specifically designed to evaluate vaccine efficacy of Varilrix, 493 children 10 to 30-month-old were followed up for a period of approximately 2.5 years after vaccination with one dose. The protective efficacy was 100% (95% CI: 80;100) against common or severe clinical cases of varicella (≥ 30 vesicles) and 88% (95% CI: 71.0; 95.2) against any serological confirmed case of varicella (at least 1 vesicle or papule).

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 (≥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.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

There is no other relevant information that has not already been stated above.

6. Pharmaceutical particulars

6.1 List of excipients

Amino acids

Human albumin

Lactose

Mannitol

Sorbitol

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

The vaccine should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 1 hour at +2℃ to +8℃ (in a refrigerator). Do not freeze.

6.4 Special precautions for storage

Store at +2℃ to +8℃ (in a refrigerator).

The lyophilised vaccine is not affected by freezing.

6.5 Nature and contents of container

Powder for reconstitution

Cream to yellowish or pinkish coloured cake or powder in 3 ml vials (Type I glass) with stopper (bromobutyl rubber) and flip-off cap (aluminium).

Solvent for reconstitution

Water for Injections in 1 ml ampoule or pre-filled syringe (Type I glass).

Packs of one.

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 peach to pink . The diluent and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical appearance prior to administration. In the event of either being observed, discard the diluent or the reconstituted vaccine.

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 water for injections diluent to the vial containing the powder. After the addition of 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 promptly.

A new needle should be used to administer the vaccine.

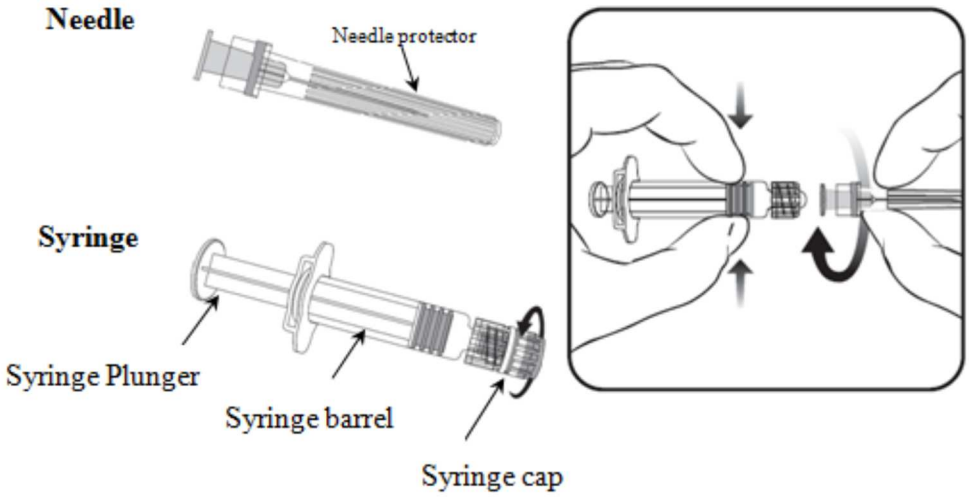
Withdraw the entire contents of the vial.

Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine since they may inactivate the virus.

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, refer to the below drawing. However, the syringe provided with Varilrix might be slightly different (without screw head) than the syringe described in the drawing. In that case, the needle should be attached without screwing.



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.

2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)

3. Remove the needle protector, which on occasion can be a little stiff.

Add the diluent to the powder. After the addition of 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 promptly.

A new needle should be used to administer the vaccine.

Withdraw the entire contents of the vial.

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

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

Vaccine :	PL 10592/0121
Diluent :	PL 10592/0021

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 25 June 2002

Date of last renewal: 12 March 2009

10. Date of revision of the text

12 September 2017

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