

# Varilrix™

## 1. NAME OF THE MEDICINAL PRODUCT

**Varilrix™**

Varicella vaccine (live, attenuated)

## 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 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.

## 3. PHARMACEUTICAL FORM

Powder and diluent for solution for injection.

## 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  $\text{mm}^3$  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).

## 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 (see 5.2 Pharmacodynamic Properties)

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 use only.

For information on instructions for preparation or reconstitution please refer to the “6.6 Instructions for use/Handling” section.

## 4.3 Contra-indications

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 contra-indicated in subjects with primary or acquired immunodeficiency states with a total lymphocyte count less than 1,200 per mm<sup>3</sup> 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).

**Varilrix™** is contra-indicated in subjects with known systemic hypersensitivity to neomycin, but a history of contact dermatitis to neomycin is not a contra-indication.

**Varilrix™** is contra-indicated during pregnancy. Furthermore, pregnancy should be avoided for three months after vaccination (see 4.6 Use During Pregnancy and Lactation).

#### **4.4 Special Warnings and Special 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.

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 and cough with respect 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. However, transmission has not been confirmed to occur in the absence of vaccine-associated cutaneous lesions in the vaccinee.

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.

**Varilrix™** should not be administered intradermally.

**Varilrix™ must under no circumstances be administered intravenously.**

#### **4.5 Interaction with Other Medicinal Products and Other Forms of Interactions**

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 contra-indication has been established.

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

#### 4.6 Pregnancy and Lactation

It is contra-indicated to administer **Varilrix™** to pregnant women. Furthermore, pregnancy should be avoided for three months after immunisation (see 4.3 Contra-indications).

There are no data regarding use in nursing women.

#### 4.7 Effect on Ability to Drive and Use Machine

Not applicable.

#### 4.8 Undesirable Effects.

##### *Clinical trials*

##### 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:	$< 1/10,000$

##### 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  $\geq 37.5$  °C or rectal temperature  $\geq 38.0$  °C)\*

Uncommon : fever (oral/axillary temperature  $> 39.0$  °C or rectal temperature  $> 39.5$  °C), fatigue, malaise

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

\*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.

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***Infections and infestations:

Herpes zoster\*\*

Immune system disorders:

Hypersensitivity, anaphylactic reactions

Nervous system disorders:

Convulsions, cerebellar ataxia\*\*

\*\*This reaction reported after vaccination is also a consequence of wild-type varicella infection. There is no indication of an increased risk of its occurrence following vaccination compared with wild-type disease.

**4.9 Overdose**

Cases of accidental administration of more than the recommended dose of **Varilrix™** have been reported. Amongst these cases, the following adverse events were reported: lethargy and convulsions. In the other cases reported as overdose there were no associated adverse events.

**5. PHARMACOLOGICAL PROPERTIES****5.1 Mechanism of Action**

**Varilrix™** produces an attenuated clinically inapparent varicella infection in susceptible subjects.

Some protection may be obtained by immunisation up to 72 hours after exposure to natural varicella.

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

## 5.2 Pharmacodynamic Properties

### Efficacy and effectiveness

The efficacy of GlaxoSmithKline's Oka/RIT varicella vaccines in preventing confirmed varicella disease (by PCR or exposure to varicella case) was evaluated in a large active controlled clinical trial in which children aged 12-22 months received one dose of *Varilrix*<sup>TM</sup> (N = 2263) or two doses of Oka/RIT containing vaccine (N = 2279). The observed vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella were respectively 65.4 % (97.5% CI: 57.2-72.1%) and 90.7% (97.5% CI: 85.9%-93.9%) after one dose of *Varilrix*<sup>TM</sup> and 94.9% (97.5% CI: 92.4-96.6%) and 99.5% (97.5% CI: 97.5-99.9%) after 2 doses of Oka/RIT containing vaccine (mean follow-up period 35 months).

In a previous study specifically designed to evaluate vaccine efficacy after one dose of *Varilrix*<sup>TM</sup>, 10 to 30-month-old children were followed up for a period of approximately 2.5 years after vaccination. The protective efficacy was 100% against common clinical cases of varicella ( $\geq 30$  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*<sup>TM</sup> 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*<sup>TM</sup> 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 (50 mIU/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 12-15 months of age, antibodies persisted for at least 7 years after vaccination with one 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 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.

### 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  $\geq 80\%$ .

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.

### **5.3 Pharmacokinetic Properties**

Evaluation of pharmacokinetic properties is not required for vaccines.

### **Clinical Studies**

See 5.2 Pharmacodynamic Properties

### **5.4 Preclinical Safety Data**

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of Excipients**

Excipients of the vaccine are: amino acids, human albumin, lactose, neomycin sulphate and polyalcohols.

Diluent is water for injection.

### **6.2 Incompatibilities**

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

### **6.3 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).

### **6.4 Special Precautions for Storage**

The lyophilised vaccine should be stored in a refrigerator between +2°C and +8°C and protected from light. The diluent can be stored in the refrigerator or at ambient temperatures. 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 6.3 Shelf Life).

### **6.5 Nature and Contents of Container**

**Varilrix™** is presented as a slightly cream to yellowish or pinkish coloured pellet in a glass vial.

The sterile diluent is clear and colourless and presented in ampoules and prefilled syringes.

### 6.6 Instructions for use/Handling

**Varilrix™** must be reconstituted by adding the contents of the supplied container of diluent to the vaccine vial. The vaccine pellet should be completely dissolved in the diluent. The entire contents of the vial are to be injected.

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

Vaccines should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

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

After reconstitution, it is recommended that the vaccine be injected as soon as possible. If not used within the recommended timeframes, the reconstituted vaccine must be discarded (see 6.3 Shelf Life).

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

Not all presentations are available in every country.

### 7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Thailand) Ltd.

### 8. MARKETING AUTHORISATION NUMBER

1C 21/40 (N).

### 9. DATE OF FIRST AUTHORISATION

28 October 1999 (unconditional license).

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