SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Varilrix powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Varilrix is a lyophilised preparation of the live attenuated varicella virus (OKA strain) produced on human diploid cell cultures.

Each 0.5 ml dose of the reconstituted vaccine contains at least $10^{3.3}$ PFU.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for injectable solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Varilrix is indicated for the active immunisation of the categories of persons listed below against varicella in the event of a negative history of varicella.

- Healthy subjects from the age of 12 months.
- Patients at high risk for severe varicella, such as patients with acute leukemia, with a chronic disorder, or under immunosuppressive treatment, or those for whom an organ transplant is planned (see also section 4.4).
- Healthy persons living in close contact with varicella patients and high-risk patients (see also section 4.4).

4.2 Posology and method of administration

Posology

Healthy subjects

Children from 12 months to 12 years of age inclusive: It is recommended that 2 doses of Varilrix be administered to children from 12 months to 12 years of age in order to ensure optimal protection against varicella. It is preferable that the second dose be administered at least 6 weeks after the first dose, but under no circumstances within a period of less than 4 weeks.

Adolescents 13 years of age or over and adults: Two doses are necessary for subjects from the age of 13. An interval of at least 6 weeks should be observed between the two doses, but in no case less than 4 weeks.
High-risk patients

The vaccination regimen described for healthy subjects is also applicable to high-risk patients, but additional doses can be necessary.

Interchangeability

A single dose of Varilrix can be administered to subjects who have already received a single dose of a vaccine containing the varicella valence.

A single dose of Varilrix can be administered followed by a single dose of another vaccine containing the varicella valence.

Method of administration

Varilrix is intended for subcutaneous injection only. The deltoid area of the arm is the preferred injection site.

For instructions on reconstitution of the medication before administration, see section 6.6.

4.3 Contra-indications

Varilrix is contra-indicated in subjects with primary or acquired immunodeficiency, who have a total lymphocyte count less than 1200 per mm$^3$ or presenting other evidence of lack of cellular immune competence, such as subjects with leukaemia, lymphomas, blood dyscrasia, clinically manifest HIV infection, or patients receiving immunosuppressive therapy (including high dose corticosteroids).

Varilrix is contraindicated in subjects who have a history of hypersensitivity to any of the constituents in the vaccine, or to neomycin. However, a history of dermatitis following contact with neomycin is not a contraindication.

Varilrix is contraindicated for pregnant women. In addition, pregnancy must be avoided in the month following vaccination.

Severe humoral or cellular immune deficiency (primary or acquired); for example, severe combined immunodeficiency, agammaglobulinaemia, and AIDS, or symptomatic infection due to HIV or with an age-dependent level of CD4+ T lymphocytes in children less than 12 months of age: CD4+ <25%; children from 12 to 35 months of age: CD4+ <20%; children 36 to 59 months of age: CD4+ <15% (see section 4.4).

Varilrix is contraindicated for patients with fructose intolerance (a rare hereditary disorder).

4.4 Special warnings and precautions for use

As for other vaccines, administration of Varilrix should be postponed in the event of acute febrile illness. The presence of a minor infection is not however a contraindication.

As for any injectable vaccine, it is recommended that an epinephrine solution be available for injection in the event of a possible anaphylactic reaction (see below, “Treatment in the event of an anaphylactic reaction”). It is generally recommended that the vaccinee be kept under medical surveillance for half an hour after vaccination.

Syncope (fainting) can occur after any vaccination, or even before, with adolescents in particular, as a psychogenic reaction to injection. This can be accompanied by several neurological signs such as transient disturbances in vision, paraesthesia and tonicoclonic movements of the limbs during the recovery phase. It is important that measures be set up to avoid injuries in the event of fainting.
Transmission of the vaccine virus has been shown to occur, but in extremely rare cases, to seronegative persons in contact with vaccinated persons. However, transmission has not been confirmed in the absence of vaccine-related skin lesions in the vaccinee.

All contact should be avoided with pregnant women susceptible to contracting varicella (especially during the first trimester of pregnancy) and with those at high-risk for developing severe varicella (such as leukaemia patients or patients receiving immunosuppressive therapy), especially when the person vaccinated develops a skin eruption within 2 to 3 weeks of immunization. If contact with these persons cannot be avoided, the potential risk of transmission of the vaccine virus should be weighed against the risk of acquiring and transmitting the wild varicella virus.

In patients receiving strongly immunosuppressive treatment, clinical varicella has appeared after vaccination. A virus resembling that of the vaccine has been detected in the vesicles. In the event of severe clinical signs, antiviral treatment is indicated.

Varilrix must not be administered intradermally, and under no circumstances intravenously.

**High-risk patients**

**Acute leukemia patients**
It has been shown that varicella constitutes a significant risk factor when it affects patients with acute leukemia. They should therefore be vaccinated if there is a negative history of varicella or in the absence of specific antibodies.

When patients are vaccinated during the acute phase of leukemia, it is necessary to interrupt chemotherapy one week before and one week after vaccination. Likewise, patients must not normally be vaccinated during the radiotherapy treatment period.

Generally, these patients are immunized when they are in complete hematological remission from the illness. It is recommended that it be ensured that the total number of lymphocytes is at least 1200 per mm³ and that there is no marked sign of cellular immunological deficiency.

**Patients receiving immunosuppressive treatment**
Patients receiving immunosuppressive treatment (including corticosteroids) for solid malignant tumors or for severe chronic illnesses (such as renal insufficiency, autoimmune diseases, collagenoses, or severe bronchial asthma) are predisposed to have severe varicella.

Generally, these patients are immunized when they are in complete hematological remission from their illness. It is recommended that it be ensured that the total number of lymphocytes is at least 1200 per mm³ and that there is no marked sign of cellular immunological deficiency.

**Patients for whom an organ transplant is planned**
If an organ transplant (for example, of a kidney) is planned, vaccination should take place several weeks before the start of immunosuppressive therapy.

**Patients with a chronic disorder**
Chronic disorders such as metabolic and endocrine imbalances, chronic pulmonary and cardiovascular disorders, mucoviscidosis and neuromuscular anomalies can also be predisposing factors for a severe varicella infection.

**Immunodeficient patients**
Vaccination may be considered in patients presenting certain immune deficiencies in whom the expected benefits are greater than the risks (for example, asymptomatic subjects infected with HIV, IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, complement deficiencies).

Immunodeficient patients presenting no contraindication to this vaccination (see section 4.3) may not respond as well as immunocompetent subjects, consequently, some of these patients may contract varicella in
the event of contact, despite appropriate administration of the vaccine. These patients should be monitored closely in order to detect any sign of varicella.

Healthy persons living in close contact with patients

To further reduce the risk of infection of high-risk subjects, it is advised that non-immune persons living in close contact with varicella patients or high-risk patients also be vaccinated. This category includes parents, brothers and sisters of high-risk subjects, medical and paramedical personnel and others who live in close contact with these patients.

4.5 Interaction with other medicinal products and other forms of interactions

The administration of Varilrix should be postponed for at least three months after the administration of immunoglobulins or after a blood transfusion, because the vaccination may not work properly due to the passively acquired varicella antibodies.

Reye’s syndrome has been reported after use of salicylates during wild varicella infections. Consequently, salicylates should not be administered in the 6 weeks following vaccination.

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. Varilrix must never be mixed with other vaccines in the same syringe. Inactivated vaccines can be administered at any time relative to the time of administration of Varilrix.

If Varilrix is administered after the measles vaccine, an interval of at least a month is recommended, as it is known that vaccination against measles can cause short-term suppression of the cellular immune response.

High-risk subjects

Varilrix should not be administered at the same time as other live attenuated vaccines. Inactivated vaccines can be administered at any time relative to the time of administration of Varilrix, given that no contraindication has been established. Different injectable vaccines should always be administered at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

Varilrix is contraindicated for pregnant women. However, no deleterious effect on the foetus has been documented after administration of varicella vaccines to pregnant women. Pregnancy should be avoided in the month following vaccination. Women intending to become pregnant should be advised to postpone their pregnancy.

Vaccinated person who develop a rash within 3 weeks after the vaccination must avoid all contact with pregnant women particularly in the first three months of pregnancy.

Lactation

No data are available on vaccination during the breastfeeding period.

4.7 Effects on ability to drive and use machines

It is very unlikely that the vaccine has an effect on the capacity to drive a vehicle or to use machines.

4.8 Undesirable effects

Healthy subjects

The safety profile presented below is based on a total of 5369 doses of Varilrix administered in monotherapy to children, adolescents and adults.
Undesirable effects with a suspected connection with the vaccine are listed below.

Frequencies are reported as follows:

- Very common (≥ 1/10)
- Common (≥1/100, < 1/10)
- Uncommon (≥ 1/1000, < 1/100)
- Rare (≥ 1/10000, < 1/1000)
- Very rare (<1/10000), including isolated cases

**Infections and infestations**
Uncommon: upper respiratory tract infection, pharyngitis

**Hematological and lymphatic system disorders:**
Uncommon: lymphadenopathy

**Psychiatric disorders:**
Uncommon: irritability

**Nervous system disorders:**
Uncommon: headache, drowsiness

**Eye disorders:**
Rare: conjunctivitis

**Respiratory, thoracic and mediastinal disorders**
Uncommon: cough, rhinitis

**Gastrointestinal disorders:**
Uncommon: nausea, vomiting.
Rare: abdominal pains, diarrhoea

**Skin and subcutaneous tissue disorders:**
Common: eruptions
Uncommon: papulo-vesicular eruptions, pruritus
Rare: urticaria

**Musculoskeletal and connective tissue disorders**
Uncommon: arthralgia, myalgia

**General problems and anomalies at the administration site**
Very common: pain at the injection site, redness
Common: swelling at the injection site*, fever (oral/axillary temperature ≥ 37.5°C; rectal temperature ≥ 38°C)*
Uncommon: fever (oral/axillary temperature ≥ 39.0°C or rectal temperature ≥ 39.5°C), fatigue, malaise.

*Swelling at the injection site and fever were very commonly reported in studies conducted in adolescents and adults. Swelling has also been reported very frequently after the second dose administered to children under the age of 13.

A tendency has been observed toward an increase in reactions of pain, redness and swelling between the first and the second injection.

No difference was noted in the reactogenicity profile between initially seropositive and initially seronegative subjects.
**High-risk patients**

There are very few data from clinical studies on patients at high risk for severe varicella. However, reactions associated with vaccination (mainly papulovesicular eruptions and fever) were usually moderate. As in healthy subjects, reactions at the injection site (redness, swelling, pain) were generally mild and transient.

**Post-marketing surveillance**

**Hematological and lymphatic system disorders**
- Thrombocytopenic purpura

**Infections and infestations**
- Herpes zoster**

**Immune system disorders**
- Hypersensitivity, anaphylactic reactions

**Nervous system disorders**
- Convulsions, cerebellar ataxia**

**These reactions reported after vaccination are also a consequence of infection by the wild varicella virus. There is no indication of an increased risk of these manifestations after vaccination compared to the risk incurred with the natural disease.**

**Treatment in the event of anaphylactic reaction**

Procedure proposed by the “Répertoire Commenté des Médicaments (Annotated Repertory of Medications)” in the event that a severe anaphylactic reaction (associated with respiratory difficulties, hypotension or shock) occurs.

Treatment is based on epinephrine (adrenalin).

Intramuscular administration is to be preferable to subcutaneous administration due to better resorption in the event of hypotension.

The dose of epinephrine:
- for an adult: 0.2 to 0.5 ml of an 1/1000 aqueous solution (= 1 mg/ml) intramuscularly
- for a child: 0.01 ml/kg of an 1/1000 aqueous solution (= 1 mg/ml) intramuscularly (max. 0.3 ml).

If there is no improvement, a second dose can be administered intramuscularly after 5 minutes.

Bronchodilator in the event of bronchospasm; I.V. corticosteroids; plasma substitute in the event of shock.

**4.9 Overdose**

Cases of accidental administration of doses higher than the recommended dose of Varilrix have been reported. Among these cases, the following secondary effects have been reported: lethargy and convulsions. In the other reported cases of overdose, there were no related secondary effects.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic category: Viral vaccine, ATC Code: J07BK 01

The presence of antibodies after vaccination is recognised as a sign of protection against the disease.
Efficacy in clinical studies

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 Priorix-Tetra six weeks apart (N = 2279) or one dose of Varilrix (N = 2263) and were followed up for a period of approximately 35 months post vaccination (long term 10-year follow-up ongoing). The observed vaccine efficacy against epidemiologically confirmed or PCR (Polymerase Chain Reaction) confirmed Varicella of any severity (defined using a prespecified scale) was 94.9% (97.5% CI: 92.4; 96.6%) after two doses of Priorix-Tetra and 65.4 % (97.5% CI: 57.2;72.1%) after one dose of Varilrix. Vaccine efficacy against moderate or severe confirmed varicella was 99.5% (97.5% CI: 97.5;99.9%) after two doses of Priorix-Tetra and 90.7% (97.5% CI: 85.9; 93.9%) after one dose of Varilrix.

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: 72;96) against any serological confirmed case of varicella (at least 1 vesicle or papule).

Actual efficiency

Data on effectiveness appear to indicate a higher level of protection and a lower incidence of cases of varicella in those patients vaccinated after 2 doses of vaccine containing the varicella valence than after a single dose.

The effectiveness of doses of Priorix-Tetra in an epidemic situation in day-care centres in Germany, where routine vaccination against varicella is recommended for children from the age of 11 months, was 91% (95% CI: 65%-98%) against the disease of any severity and was 94% (95% CI: 54%-99%) against the moderate disease.

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.

Immune response

Healthy subjects

In children 11 months to 21 months of age, the seroconversion rate measured with ELISA, Enzygnost, Dade Behring (50 mIU/ml) six weeks after administration of a dose of vaccine reaches 89.6%, and 100% after administration of a second dose of vaccine.

In children from 9 months to 12 years, of age inclusive the seroconversion rate measured by immunoflorescence six weeks after administration of a dose of vaccine exceeded 98 %. In children from 12 to 15 months of age, antibodies persisted for at least 7 years after vaccination with a dose.

In children from 9 months to 6 years of age, the seroconversion rate measured by immunoflorescence six weeks after administration of a second dose of vaccine was 100%. An appreciable increase in antibody titers was observed after administration of a second dose (the GMT increased by a factor of 5 to 26).

In subjects 13 years of age and over, the seroconversion rate measured by immunoflorescence six weeks after administration of a second dose of vaccine was 100%. One year after vaccination, all the subjects tested were still seropositive.

In clinical studies, efficacy data show a higher level of protection and a reduction in the number of varicella cases appearing after administration of two doses of vaccine instead of a single dose.
**High-risk patients**

In high-risk patients, seroconversion was 80\% but in leukemic patients it reached approximately 90\%.

In high-risk patients, periodic measurement of varicella antibodies after vaccination may be indicated to identify those for whom revaccination could be beneficial.

In one study, a lower incidence of herpes zoster in vaccinated leukaemic patients than in non-vaccinated leukaemic patients infected naturally.

Transmission of the vaccine virus between immunodepressed brothers and sisters has been demonstrated but the cutaneous manifestations were very mild in the child infected.

Some protection can be obtained by vaccination up to 72 hours after exposure to wild varicella.

**5.2 Pharmacokinetic properties**

Evaluation of pharmacokinetic properties is not required for vaccines.

**5.3 Data on preclinical innocuity**

Not relevant.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Powder: lactose, sorbitol, manniol, amino acids
Solvent: Water for injectable preparations.

**6.2 Incompatibility**

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

**6.3 Shelf-life**

2 years.

The reconstituted vaccine can be kept for 90 minutes maximum at room temperature (25° C) or kept in a refrigerator (+2° - +8°C) for 8 hours maximum. If the reconstituted vaccine is not used within these periods of time, it should be discarded.

**6.4 Special precautions for storage**

Varilrix should be kept in a refrigerator (between 2°C and 8°C).

The limiting date for use is the last day of the month printed on the packaging after the letters EXP.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

**6.5 Nature and contents of container**

Box containing a single-dose vial of vaccine accompanied with a pre-filled syringe or an ampoule of solvent. The containers are of Type I, neutral glass (European Pharmacopeia).

The powder or pellet of vaccine contained in the vial is slightly cream-coloured to yellowish or pinkish. The solvent contained in the syringe or the ampoule is limpid and colourless.
Not all pack sizes may be marketed.

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 pellet 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.

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

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

7. MARKETING AUTHORIZATION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut, 89
1330 Rixensart
Belgium

8. MARKETING AUTHORIZATION NUMBER

MA170/00801

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

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10. DATE OF REVISION/APPROVAL OF THE TEXT

28-05-18