SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT
Varilrix®, 10³³ 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* 10³³ 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 in healthy adults and adolescents (≥ 13 years) who have been found to be seronegative with respect to the varicella-zoster virus and are, therefore, at risk of developing chickenpox.

Varilrix is not indicated for routine use in children. However, it may be administered to seronegative healthy children of 1-12 years of age who are close contacts (e.g. household) of persons considered to be at high risk of severe varicella infections.

4.2 Posology and Method of Administration

Posology

Children 1-12 years, adolescents (≥ 13 years) and adults
Two doses (each of 0.5 ml of reconstituted vaccine) should be given, with an interval between doses of at least 6 weeks but in no circumstances less than 4
weeks. One dose of Varilrix may be administered after a first dose of another varicella containing vaccine (see section 5.1).

There are insufficient data to determine the long-term protective efficacy of the vaccine. However, there is currently no evidence that further doses are routinely required following completion of a two-dose regimen in healthy adolescents and adults (see section 5.1).

If Varilrix is to be administered to seronegative subjects before a period of planned or possible future immunosuppression (such as those awaiting organ transplantation and those in remission from malignant disease), the timing of the vaccinations should take into account the delay after the second dose before maximal protection might be expected (see also sections 4.3, 4.4 and 5.1).

Varilrix should not be administered to children aged less than one year.

**Elderly**

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

**Method of administration**

Varilrix is for subcutaneous administration only. The upper arm (deltoid region) is the preferred site of injection.

Varilrix should not be administered intradermally.

**Varilrix must under no circumstances be administered intravascularly.**

Varilrix must not be mixed with any other medicinal product in the same syringe (see also sections 4.5 and 6.2).

**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).

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).

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.

Varilrix contains a live attenuated varicella-zoster virus and administration is contra-indicated during pregnancy (see sections 4.3 and 4.6). Due to an unknown degree of risk to the mother and to the fetus, female candidates for vaccination must be advised to take adequate precautions to prevent pregnancy occurring between the two doses and for three months after the second dose.

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 and has not been confirmed to occur in the absence of vaccine-associated cutaneous lesions in the vaccinee (see section 4.8).

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 seronegative children 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.

4.5 Interactions with other Medicaments and other Forms of Interaction

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 Pregnancy and Lactation

Pregnancy
Varicella-zoster virus may cause severe clinical disease in pregnant individuals and may adversely affect the fetus and/or result in perinatal varicella, depending on the gestational stage when the infection occurs. Because the possible effects of infection with the vaccine viral strain on the mother and on the fetus are unknown, Varilrix must not be administered to pregnant women.

Furthermore, female candidates for vaccination must be advised to take adequate precautions to avoid pregnancy occurring between the two vaccine doses and for three months following the second dose.

Lactation
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.

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 Un desirable 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:** ≥10%
- **Common:** ≥1% and <10%
- **Uncommon:** ≥0.1% and <1%
- **Rare:** ≥0.01% and <0.1%
- **Very rare:** <0.01%

**Blood and lymphatic system disorders**
- Uncommon: lymphadenopathy

**Nervous system disorders**
- Uncommon: headache, somnolence
- Very rare: dizziness

**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

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

**General disorders and administration site conditions**
- Very common: pain, redness and swelling at the injection site*, fever (oral/axillary temperature ≥ 37.5°C or rectal temperature ≥ 38.0°C)*
- Uncommon: fever (oral/axillary temperature > 39.0°C or rectal temperature > 39.5°C), fatigue, malaise
- Very rare: face oedema

**Psychiatric disorders**
- Uncommon: irritability
Swelling at the injection site and fever were commonly reported in studies conducted in children ≤ 12 years.

In general, the reactogenicity profile after the second dose was comparable to that after the first dose. However, the rates of injection site reactions (primarily redness and swelling) were higher after the second dose in children aged ≤12 years.

No differences were seen in the reactogenicity profile between initially seropositive and initially seronegative subjects.

**Post-marketing surveillance**

* Nervous system disorders
  Febrile and non-febrile convulsions, cerebellar ataxia**

* Infections and infestations
  Herpes zoster**

* Immune system disorders
  Hypersensitivity, anaphylactic reactions

** 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.

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

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.

In clinical trials, the immune response to vaccination was routinely measured using an immunofluorescence assay. Antibody titres of $\geq 1:4$ (the detection level of the test) were considered as positive.

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 ($\geq 98.7\%$) children aged 9 months to 12 years tested had antibody levels $\geq 4$ (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 $\geq 4$ (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 ($\geq 13$ 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
6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Amino acids  
Human albumin  
Lactose  
Neomycin sulphate  
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°C to +8°C (in a refrigerator). Do not freeze.

6.4 Special Precautions for Storage

Store at +2°C to +8°C (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 (Type I glass).

Packs of one.
6.6 **Special precautions for disposal and 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.

Varilrix must be reconstituted by adding the contents of the supplied container of water for injections diluent to the vial containing the pellet. After the addition of the diluent to the pellet, the mixture should be well shaken until the pellet is completely dissolved in the diluent.

Biochemical and physical in-use stability has been demonstrated on the reconstituted vaccine for 90 minutes at room temperature or for 8 hours at 2°C-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 8 hours at 2°C-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

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 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**

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
25 June 2002

10. DATE OF REVISION OF THE TEXT
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