

## Name of Medicine

### **VARIVAX<sup>®</sup>**

*Varicella Virus Vaccine Live (Oka/Merck)*

0.5 mL single dose vial

## Presentation

VARIVAX when reconstituted is a clear, colourless to pale yellow liquid. Each 0.5 mL dose contains not less than 1350 plaque forming units of varicella virus (Oka/Merck).

## Therapeutic Class

VARIVAX is live, attenuated virus vaccine (a lyophilised preparation of the Oka/Merck strain of varicella).

## Indications

VARIVAX is indicated for vaccination against varicella in individuals 12 months of age and older.

## Revaccination

The duration of protection of refrigerator-stable VARIVAX is unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination. In addition, a boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella as well as following a second dose of varicella vaccine (Oka/Merck).

In a highly vaccinated population, immunity for some individuals may wane due to lack of exposure to wild-type varicella as a result of shifting epidemiology. Post-marketing surveillance studies are ongoing to evaluate the need and timing for booster vaccination.

Vaccination with VARIVAX may not result in protection of all healthy, susceptible children, adolescents, and adults.

## Dosage and Administration

### **For Subcutaneous Administration**

Do not inject intravenously.

Children 12 months to 12 years of age should receive a 0.5 mL dose administered subcutaneously. A second dose of VARIVAX administered at least 3 months later is recommended to ensure optimal protection against varicella.

Adolescents and adults 13 years of age and older should receive a 0.5 mL dose administered subcutaneously at elected date and a second 0.5 mL dose 4 to 8 weeks later.

The outer aspect of the upper arm (deltoid region) is the preferred site of injection.

### Method of administration

To reconstitute the vaccine, use only the diluent supplied with the vaccine (sterile water for injection BP) since it is free of preservatives or other anti-viral substances which might

inactivate the vaccine virus. It may be supplied in the same carton in which case it should be refrigerated. If the diluent is supplied separately it may be stored at room temperature (20°C to 25°C, 68°F to 77°F), or in the refrigerator.

To reconstitute the vaccine, first withdraw 0.7 mL of diluent into the syringe to be used for reconstitution. Inject all of the diluent in the syringe into the vial of lyophilised vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume (about 0.5 mL) of reconstituted vaccine subcutaneously, preferably into the outer aspect of the upper arm (deltoid region) or the anterolateral thigh. **It is recommended that the vaccine be administered immediately after reconstitution, to minimise loss of potency. Discard if reconstituted vaccine is not used within 150 minutes.**

**Do not freeze reconstituted vaccine.**

**Caution:** A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of VARIVAX because these substances may inactivate the vaccine virus.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one individual to another.

Parenteral medicine products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. VARIVAX when reconstituted is a clear, colourless to pale yellow liquid.

## **Contraindications**

History of hypersensitivity to any component of the vaccine, including gelatin.

History of anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin).

Blood dyscrasias, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Immunosuppressive therapy (including high-dose corticosteroids); however, VARIVAX is not contraindicated for use with topical corticosteroids or low-dose corticosteroids, as are commonly used for asthma prophylaxis. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Vaccination with live attenuated varicella vaccine can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids.

Primary and acquired immunodeficiency states, including immunosuppression in association with AIDS or other clinical manifestations of infection with human immunodeficiency virus, except immunosuppression in asymptomatic children with CD4 T-lymphocyte percentages  $\geq 25\%$ .

Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Active untreated tuberculosis.

Any active febrile illness with fever  $>38.5^{\circ}\text{C}$  ( $>101.3^{\circ}\text{F}$ ) however, low-grade fever itself is not a contraindication to vaccination.

Pregnancy; the possible effects of the vaccine on foetal development are unknown at this time. However, wild-type varicella is known to sometimes cause foetal harm. If vaccination of post pubertal females is undertaken, pregnancy should be avoided for three months following vaccination (See Warnings and Precautions, *Pregnancy*).

## **Warnings and Precautions**

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactoid reaction occur.

The duration of protection from varicella infection after vaccination with VARIVAX is unknown.

The safety and efficacy of VARIVAX have not been established in children and young adults who are known to be infected with human immunodeficiency viruses with and without evidence of immunosuppression (see also Contraindications).

## **Transmission**

Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from vaccinees who do not develop a varicella-like rash has also been reported.

Therefore, vaccine recipients should attempt to avoid, whenever possible, close association with susceptible high risk individuals for up to six weeks. In circumstances where contact with high risk individuals is unavoidable, the potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus. Susceptible high risk individuals include:

- immunocompromised individuals
- pregnant women without documented history of chickenpox or laboratory evidence of prior infection
- newborn infants of mothers without documented history of chickenpox or laboratory evidence of prior infection.

## **Pregnancy**

There are no adequate and well-controlled studies in pregnant women. It is not known whether VARIVAX can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, VARIVAX should not be administered to pregnant females, furthermore, pregnancy should be avoided for three months following vaccination (see Contraindications).

## **Nursing Mothers**

It is not known whether varicella vaccine virus is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if VARIVAX is administered to a nursing woman.

## **Paediatric Use**

No clinical data are available on safety or efficacy of VARIVAX in children less than one year of age. Administration to infants under twelve months of age is not recommended.

## Animal Toxicology

### Carcinogenesis, Mutagenesis, Reproduction

VARIVAX has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

## Adverse Effects

### Clinical Studies

In clinical trials, varicella vaccine (Oka/Merck) was administered to approximately 17,000 healthy children, adolescents and adults. Varicella vaccine (Oka/Merck) was generally well tolerated.

In a double-blind placebo-controlled study among 956 healthy children and adolescents, 914 of whom were serologically confirmed to be susceptible to varicella, the only adverse reactions that occurred at a significantly ( $p < 0.05$ ) greater rate in vaccine recipients than in placebo recipients were pain and redness at the injection site and varicella-like rash.

### Children 1 to 12 Years of Age

#### One Dose Regimen in Children

In clinical trials involving healthy children monitored for up to 42 days after a single dose of varicella vaccine (Oka/Merck), the frequency of fever, injection-site complaints, or rashes were reported as follows:

Reaction	N	Post dose 1	Peak Occurrence in Post-vaccination Days
Fever $\geq 102^{\circ}\text{F}$ ( $39^{\circ}\text{C}$ ) Oral	8824	14.7%	0-42
Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, haematoma, induration, stiffness)	8913	19.3%	0-2
Varicella-like rash (injection site) Median number of lesions	8913	3.4% 2	8-19
Varicella-like rash (generalised) Median number of lesions	8913	3.8% 5	5-26

In addition, the most frequently ( $\geq 1\%$ ) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, cough, irritability/nervousness, fatigue, disturbed sleep, diarrhoea, loss of appetite, vomiting, otitis, diaper rash/contact rash, headache, teething, malaise, abdominal pain, other rash, nausea, eye complaints, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions (including allergic rash, hives), stiff neck, heat rash/prickly heat, insect bites, arthralgia, eczema/dry skin/dermatitis, constipation, itching.

Pneumonitis has been reported rarely ( $< 1\%$ ) in children vaccinated with varicella vaccine (Oka/Merck); a causal relationship has not been established.

Febrile seizures have occurred rarely ( $< 0.1\%$ ) in children vaccinated with varicella vaccine (Oka/Merck); a causal relationship has not been established.

### Two Dose Regimen in Children

In a clinical trial involving healthy children who received two doses of varicella vaccine (Oka/Merck) 3 months apart and were monitored for up to 42 days after any dose, the frequency of fever, injection-site complaints, rashes, and systemic clinical complaints are reported in Table 2. The 2-dose regimen of varicella vaccine was generally well tolerated, with a safety profile generally comparable to that of the 1-dose regimen.

<b>Table 2 Fever, Local Reactions or Rashes (%) in Children 0 to 42 Days</b>				
Reaction	<u>N</u>	Post dose 1 (n=1102)	N	Post dose 2 (n=1022)
Fever $\geq 38.9^{\circ}\text{C}$	<u>1077</u>	14.3%	975	10.5%
Injection site complaints (soreness, erythema, swelling, varicella like rash, pruritus, ecchymosis, hematoma, induration, pyrexia)	1081	25.7%	981	25.8%
Varicella like rash, injection site	1081	3.7%	981	1.6%
Varicella like rash, generalised	1081	3.4%	981	1.2%
Systemic clinical complaints	1081	85.8%	981	66.3%

*n* = Number of subjects who received the indicated injection

*N* = number of subjects with follow-up data for the indicated category following both Dose 1 and Dose 2

### **Adolescents and Adults 13 Years of Age and Older**

In clinical trials involving healthy adolescents and adults, the majority of whom received two doses of varicella vaccine (Oka/Merck) and were monitored for up to 42 days after any dose, the frequency of fever, injection-site complaints, or rashes were reported as follows:

<b>Table -3 Fever, Local Reactions, or Rashes (%) in Adolescents and Adults 0 to 42 Days Post-vaccination</b>						
Reaction	N	Post Dose 1	Peak Occurrence in Post-vaccination Days	N	Post Dose 2	Peak Occurrence in Post-vaccination Days
Fever $\geq 100^{\circ}\text{F}$ ( $37.8^{\circ}\text{C}$ ) Oral	1584	10.2%	14-27	956	9.5%	0-42
Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, haematoma, induration, numbness)	1606	24.4%	0-2	955	32.5%	0-2
Varicella-like rash (injection site)	1606	3.1%	6-20	955	1.0%	0-6
Median number of lesions		2			2	

Varicella-like rash (generalised)	1606	5.5%	7-21	955	0.9%	0-23
Median number of lesions		5			5.5	

In addition, the most frequently ( $\geq 1\%$ ) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, irritability/nervousness, diarrhoea, stiff neck, lymphadenopathy, chills, eye complaints, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, constipation, lower respiratory illness, allergic reactions (including allergic rash, hives), contact rash, cold/canker sore, dizziness and insect bites.

### **Post-Marketed Clinical Studies**

In a post-marketing study conducted to evaluate short-term safety (follow-up of 30 or 60 days) in approximately 86,000 children, 12 months to 12 years of age, and in approximately 3600 adolescents and adults, 13 years of age and older, varicella vaccine (Oka/Merck) was generally well tolerated. No serious vaccine-related adverse events were reported.

As with any vaccine, there is the possibility that broad use of the vaccine could reveal adverse reactions not observed in clinical trials.

### **Post-Marketed Experience**

The following additional adverse effects have been reported regardless of causality since the vaccine has been marketed:

*Body As A Whole:* Anaphylaxis (including anaphylactic shock) and related phenomena such as angioneurotic oedema, facial oedema, and peripheral oedema; anaphylaxis in individuals with or without an allergic history.

*Eye Disorders:* Necrotizing retinitis (reported only in immunocompromised individuals).

*Gastrointestinal Disorders:* Nausea, vomiting

*Haemic and Lymphatic System:* Aplastic anaemia, thrombocytopaenia (including idiopathic thrombocytopaenic purpura [ITP]), lymphadenopathy.

*Infections and Infestations:* Varicella (vaccine strain)

*Nervous/Psychiatric:* Encephalitis; cerebrovascular accident; transverse myelitis; Guillain-Barré syndrome; Bell's palsy; ataxia; febrile and non-febrile seizures; aseptic meningitis; dizziness; paresthesia, irritability.

*Respiratory:* Pharyngitis; pneumonia/pneumonitis; upper respiratory tract infection..

*Skin:* Stevens-Johnson syndrome; erythema multiforme; Henoch-Schönlein purpura; secondary bacterial infections of skin and soft tissue, including impetigo and cellulitis; herpes zoster.

### **Interactions**

Vaccination should be deferred for at least 5 months following blood or plasma transfusions, or administration of immune globulin or varicella zoster immune globulin (VZIG).

Following administration of VARIVAX, any immune globulin including VZIG should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination.

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection.

Results from clinical studies indicate that VARIVAX can be administered concomitantly with M-M-R<sup>®</sup> II (Measles, Mumps and Rubella Virus Vaccine Live), or COMVAX<sup>®</sup> (*Haemophilus influenzae* type b conjugate and hepatitis B vaccine). If VARIVAX is not given concomitantly with M-M-R II, a 1-month interval between the 2 live virus vaccines should be observed.

Limited data from an experimental product containing varicella vaccine suggest that VARIVAX can be administered concomitantly with DTaP (diphtheria, tetanus, acellular pertussis) using separate sites and syringes and with OPV (oral poliovirus vaccine).

## **Overdosage**

There are no data with regard to overdose.

## **Actions**

### **Summary of clinical trial data**

#### Two Dose Regimen in Children

In a clinical trial, a total of 2216 children 12 months to 12 years of age with a negative history of varicella were randomized to receive either 1 dose of VARIVAX (n=1114) or 2 doses of VARIVAX (n=1102) given 3 months apart. Subjects were actively followed for varicella, any varicella-like illness, or herpes zoster and any exposures to varicella or herpes zoster on an annual basis for 10 years after vaccination. Persistence of VZV antibody was measured annually for 9 years. Most cases of varicella reported in recipients of 1 dose or 2 doses of vaccine were mild. The estimated vaccine efficacy for the 10-year observation period was 94% for 1 dose and 98% for 2 doses (p<0.001). This translates to a 3.4-fold lower risk of developing varicella >42 days postvaccination during the 10-year observation period in children who received 2 doses than in those who received 1 dose (2.2% vs. 7.5%, respectively).

### **Immunogenicity of Varicella Vaccine (Oka/Merck)**

Clinical trials with several formulations of the vaccine containing attenuated virus ranging from 1000 to 50,000 PFU per dose have demonstrated that varicella vaccine (Oka/Merck) induces detectable humoral immune responses in a high proportion of individuals and is generally well tolerated in healthy individuals ranging from 12 months to 55 years of age.

Varicella vaccine (Oka/Merck) induces both humoral and cell-mediated immune responses in vaccinees. The relative contributions of humoral immunity and cell-mediated immunity to protection from chickenpox are unknown.

The following section presents immunogenicity data on a 1-dose regimen and a 2-dose regimen in children, and a 2-dose regimen in adolescents and adults.

#### One Dose Regimen in Children

Seroconversion as defined by the acquisition of any detectable varicella antibodies (based on assay cut off that generally corresponds to 0.6 units in the gpELISA, a highly sensitive

assay which is not commercially available) was observed in 98% of vaccinees at approximately 4 to 6 weeks post-vaccination in 9610 susceptible children 12 months to 12 years of age who received doses ranging from 1000 to 50,000 PFU. Rates of breakthrough disease were significantly lower among children with varicella antibody titres  $\geq 5$  gpELISA units compared to children with titres  $< 5$  gpELISA units. Titres  $\geq 5$  gpELISA units were induced in approximately 83% of children vaccinated with a single dose of vaccine at 1000 to 50,000 PFU per dose. The immune response rate to varicella vaccine (Oka/Merck) (as determined by the percentage of subjects with varicella antibody titres  $\geq 5$  gpELISA units at 6 weeks post-vaccination, an approximate correlation of protection) in subjects participating in follow-up studies ranged from 72 to 98%.

#### Two Dose Regimen in Children

In a multicenter study, healthy children 12 months to 12 years of age received either 1 dose of VARIVAX or 2 doses administered 3 months apart. The immunogenicity results are shown in the following table.

<b>Table 4</b>			
<b>Immunogenicity of One and Two Dose Regimens in Children</b>			
<b>0 to 42 Days Post-vaccination</b>			
	<b>VARIVAX</b> <b>1-Dose Regimen</b> (N = 1114)	<b>VARIVAX</b> <b>2-Dose Regimen</b> (N = 1102)	
	6 Weeks Postvaccination	6 Weeks Postdose 1	6 Weeks Postdose 2
Seroconversion Rate	98.9% (882/892)	99.5% (847/851)	99.9% (768/769)
Percent with VZV Antibody Titre $\geq 5$ gpELISA units/mL (Seroprotection Rate)	84.9% (757/892)	87.3% (743/851)	99.5% (765/769)
Geometric mean titres (gpELISA units/mL)	12.0	12.8	141.5

The results from this study and other studies in which a second dose of vaccine was administered 3 to 6 years after the initial dose demonstrate significant boosting of the VZV antibody response with a second dose. VZV antibody levels after 2 doses given 3 to 6 years apart are comparable to those obtained when the 2 doses are given 3 months apart.

#### Two Dose Regimen in Adolescents and Adults

In a multicentre study involving susceptible adolescents and adults 13 years of age and older, two doses of varicella vaccine (Oka/Merck) administered four to eight weeks apart induced a seroconversion rate (gpELISA  $\geq 0.6$  units) of approximately 75% in 539 individuals four weeks after the first dose and of 99% in 479 individuals four weeks after the second dose. The average antibody response in vaccinees who received the second dose eight weeks after the first dose was higher than that in those who received the second dose four weeks after the first dose. In another multicentre study involving adolescents and adults, two doses of varicella vaccine (Oka/Merck) administered eight weeks apart induced a seroconversion rate (gpELISA  $\geq 0.6$  units) of 94% in 142 individuals six weeks after the first dose and 99% in 122 individuals six weeks after the second dose.

### **Persistence of Immune Response**



The following section presents immune persistence data on a 1-dose regimen and a 2-dose regimen in children, and a 2-dose regimen in adolescents and adults.

### One Dose Regimen in Children

In those clinical studies involving healthy children who have been followed long-term post single-dose vaccination, detectable varicella antibodies (gpELISA  $\geq 0.6$  units) were present in 99.1% (3092/3120) at 1 year, 99.4% (1382/1391) at 2 years, 98.7% (1032/1046) at 3 years, 99.3% (997/1004) at 4 years, 99.2% (727/733) at 5 years, and 100% (432/432) at 6 years post-vaccination.

### Two Dose Regimen in Children

Over 9 years of follow-up, the GMTs (geometric mean titre) and percent of subjects with VZV antibody titres  $\geq 5$  gpELISA units/mL in the 2-dose recipients were higher than those in the 1-dose recipients for the first year of follow-up and comparable during the entire follow-up period. The cumulative rate of VZV antibody persistence with both regimens remained very high at year 9 (99.0% for the 1-dose group and 98.8% for the 2-dose group).

### Two Dose Regimen in Adolescents and Adults

In clinical studies involving healthy adolescents and adults who received 2 doses of vaccine, detectable varicella antibodies (gpELISA  $\geq 0.6$  units) were present in 97.9% (568/580) at 1 year, 97.1% (34/35) at 2 years, 100% (144/144) at 3 years, 97.0% (98/101) at 4 years, 97.5% (78/80) at 5 years, and 100% (45/45) at 6 years post-vaccination.

A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella which could account for the apparent long-term persistence of antibody levels after vaccination in these studies. The duration of protection from varicella obtained using varicella vaccine (Oka/Merck) in the absence of wild-type boosting is unknown.

## **Pharmacokinetics**

Nil

## **Medicine Classification**

Prescription Medicine.

## **Package Quantities**

VARIVAX is available in either a single dose carton containing a vial of vaccine and a vial of diluent or in a carton of 10 doses of vaccine with a corresponding carton containing 10 doses of diluent.

## **Pharmaceutical Precautions**

### **Stability**

VARIVAX has a minimum potency level of approximately 1350 PFU 150 minutes after reconstitution at room temperature (20°C to 25°C, 68°F to 77°F).

## Storage

### Vaccine Vial

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 2°C to 8°C or colder (36°F to 46°F or colder), but not exceed temperatures lower than -50°C (-58°F). Use of dry ice may subject VARIVAX to temperatures colder than -50°C (-58°F).

Before reconstitution, VARIVAX has a shelf-life of 24 months when refrigerated at 2°C to 8°C or colder (36°F to 46°F or colder). The vaccine may also be stored in a freezer, if subsequently transferred to a refrigerator, **the vaccine should not be refrozen.**

Before reconstitution, protect from light.

**Discard if reconstituted vaccine is not used within 150 minutes (2½ hours).**

### Vial of diluent

The vial of diluent should be stored separately at room temperature (20°C to 25°C, 68°F to 77°F) or in the refrigerator if it is supplied in a separate carton to the vaccine.

### Combination pack with vaccine vial and diluent

For combination packs with vaccine vial and diluent packaged together, store in the refrigerator at 2°C to 8°C (36°F to 46°F). **DO NOT STORE THE COMBINATION PACK IN THE FREEZER.**

## Further Information

### Ingredients

#### Active Ingredients

Each 0.5 mL dose of VARIVAX contains: a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus when reconstituted as directed and stored at room temperature for 30 minutes.

#### Inactive Ingredients

Each 0.5 mL dose contains: approximately 18 mg of sucrose, 8.9 mg of hydrolysed gelatin, 3.6 mg of urea, 2.3 mg of sodium chloride, 0.36 mg of monosodium L-glutamate, 0.33 mg of sodium phosphate dibasic, 57 mcg of potassium phosphate monobasic, 57 mcg of potassium chloride. The product also contains residual components of MRC-5 cells and trace quantities of neomycin and bovine calf serum from MRC-5 culture media. The product contains no preservative.

## Name and Address

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## **Date of Preparation**

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