

AUSTRALIAN PRODUCT INFORMATION – VARIVAX[®] Refrigerated Varicella Virus Vaccine Live

1 NAME OF THE MEDICINE

Varicella Virus Vaccine Live (Oka/Merck)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION and

3 PHARMACEUTICAL FORM

VARIVAX Refrigerated [Varicella Virus Vaccine Live (Oka/Merck)] is a lyophilised preparation of the Oka/Merck strain of live, attenuated varicella virus. The virus was initially obtained from a child with wild-type varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus for varicella vaccine was performed at Merck Research Laboratories in human diploid cell cultures (MRC-5) that were free of adventitious agents.

VARIVAX Refrigerated, when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.5 mL dose contains: a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus when reconstituted and stored at room temperature for 150 minutes (2 ½ hours).

Powder for Injection

VARIVAX Refrigerated when reconstituted is a clear, colourless to pale yellow liquid.

List of excipients with known effect: This vaccine may contain trace quantities of neomycin.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

The product also contains residual components of MRC-5 cells and trace quantities of neomycin, and bovine serum from MRC-5 culture media. The product contains no preservative.

The manufacture of this product includes exposure to bovine derived material. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

See the Australian NHMRC Immunisation Handbook for vaccination recommendations and schedule.

Groups who would particularly benefit from vaccination include:

- Non-immune adults, especially those in at-risk occupations such as health-care workers, teachers and workers in children's day-care centres.
- Non-immune parents of young children
- Non-immune household contacts, both adults and children, of immunocompromised patients with no history of disease.

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 Refrigerated may not result in protection of all healthy, susceptible children, adolescents and adults (see Section 5 PHARMACOLOGICAL PROPERTIES).

4.2 DOSE AND METHOD OF ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION.

VARIVAX Refrigerated should not be administered intravenously or intradermally.

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) is the preferred site of injection.

Methods of administration

The diluent should be stored separately at room temperature (20°C to 25°C, 68°F to 77°F) or in the refrigerator.

Vial of diluent

To reconstitute the vaccine, first withdraw 0.7 mL of diluent into the syringe to be used for reconstitution. Inject all 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) or the anterolateral thigh.

Pre-filled syringe of diluent

To reconstitute the vaccine, inject the entire contents of the pre-filled diluent 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) 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 (2½ HOURS)

CAUTION: A sterile syringe free of preservatives, antiseptics and detergents should be used for each injection and/or reconstitution of VARIVAX Refrigerated 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.

To reconstitute the vaccine, use only the diluent supplied (Sterile Diluent for Merck, Sharp & Dohme Live Virus Vaccines), since it is free of preservatives or other anti-viral substances which might inactivate the vaccine virus.

DO NOT FREEZE RECONSTITUTED VACCINE.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

4.3 CONTRAINDICATIONS

A history of hypersensitivity to any component of the vaccine, including gelatin.

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

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Individuals receiving immunosuppressive therapy. 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.

Individuals with primary and acquired immunodeficiency states, including those who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency virus; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

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

Active untreated tuberculosis.

Any febrile respiratory illness or other active febrile infection.

Pregnancy; the possible effects of the vaccine on fetal development are unknown at this time. However, wild-type varicella is known to sometimes cause fetal harm. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Adequate treatment provisions should be available for immediate use should an anaphylactoid reaction occur.

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

It is not known whether VARIVAX Refrigerated given immediately after exposure to wild-type

varicella virus will prevent illness.

The safety and efficacy of VARIVAX Refrigerated have not been established in children or young adults who are known to be infected with human immunodeficiency viruses with and without evidence of immunosuppression (see also Section 4.3 CONTRAINDICATIONS).

VARIVAX Refrigerated should not be administered intravenously or intradermally. VARIVAX Refrigerated should not be mixed with other vaccines in the same syringe.

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 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

Use in the elderly

No data available

Paediatric use

No clinical data are available on safety or efficacy of VARIVAX Refrigerated in children less than one year of age. Administration to infants under 12 months of age is not recommended.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 Refrigerated, 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 Refrigerated as Reye Syndrome has been reported following the use of salicylates during wild-type varicella infection.

Results from clinical studies indicate that VARIVAX Refrigerated can be administered concomitantly with M-M-R*II (Measles, Mumps and Rubella Virus Vaccine Live), a combined vaccine of *Haemophilus influenzae type b*, diphtheria and tetanus and pertussis or COMVAX (*Haemophilus influenzae type b* conjugate and hepatitis B vaccine). When varicella vaccine (Oka/Merck) was given 6 weeks after the combined vaccine of *Haemophilus influenzae type b*, diphtheria, tetanus and pertussis the GMT for varicella antibody was 14.5 gpELISA units

compared with 10.5 for those given varicella vaccine (Oka/Merck) concomitantly with the combined vaccine of *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis. There was little difference in seroconversion rates between the 2 groups.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

VARIVAX Refrigerated has not been evaluated for its potential to impair fertility.

Use in pregnancy (Category B2)

Currently available live attenuated virus vaccines have not caused teratogenic effects in humans. There are no adequate and well controlled studies in pregnant women. It is not known whether VARIVAX Refrigerated can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, VARIVAX Refrigerated should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see Section 4.3 CONTRAINDICATIONS).

Use in lactation

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 Refrigerated is administered to a nursing woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Studies

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

In a double-blind placebo controlled study among 914 healthy children and adolescents who 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 an earlier formulation of varicella vaccine (Oka/Merck) the frequency of fever, injection-site complaints or rashes were reported as follows:

Table 1
Fever, Local Reactions or Rashes (%)
in Children
0 to 42 Days Postvaccination

Reaction	N	Post dose 1	Peak Occurrence in Postvaccination Days
Fever $\geq 39^{\circ}\text{C}$ Oral	8824	14.7%	0-42
Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, 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 (generalized) 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, nappy 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.

Clinical safety of VARIVAX Refrigerated (n=635) was compared with that of the previously licensed formulation of VARIVAX (n=323) for 42 days postvaccination in US children 12 to 23 months of age. The safety profiles were comparable for the two different formulations. Pain/tenderness/soreness (24.8 to 28.9%) and erythema (18.4 to 21.0%) were the most commonly reported local reactions. The most common systemic adverse events (reported by $\geq 10\%$ of subjects in one or more treatment groups, irrespective of causal relationship to vaccination) were: fever $\geq 38.9^{\circ}\text{C}$, oral equivalent (27.0 to 29.2%), upper respiratory infection (26.9 to 29.7%), otitis media (12.0 to 14.1%), cough (11.0 to 15.1%), rhinorrhea (8.7 to 10.6%), and irritability (6.5 to 11.9%). Six subjects reported serious adverse experiences; all were judged by the investigators as being unrelated to vaccination.

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.

Table 2
Fever, Local Reactions or Rashes (%)
in Children
0 to 42 Days

Reaction	N	Post dose 1	N	Post dose 2
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		(n=1102)		(n=1022)
Fever $\geq 38.9^{\circ}\text{C}$	1077	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) of an earlier formulation of the vaccine, and were monitored for up to 42 days after any dose, the frequency of fever, injection-site complaints or rashes were reported as follows:

Table 3
Fever, Local Reactions or Rashes (%) in
Adolescents and Adults
0 to 42 Days Postvaccination

Reaction	N	Post Dose 1	Peak Occurrence in Post-vaccination Days	N	Post Dose 2	Peak Occurrence in Post-vaccination Days
Fever $\geq 37.7^{\circ}\text{C}$ Oral	1584	10.2%	14-27	956	9.5%	0-42
Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness)	1606	24.4%	0-2	955	32.5%	0-2
Varicella-like rash (injection site) Median number of lesions	1606	3.1% 2	6-20	955	1.0% 2	0-6
Varicella-like rash (generalised) Median number of lesions	1606	5.5% 5	7-21	955	0.9% 5.5	0-23

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-Marketing Clinical Studies

In a post-marketing study conducted to evaluate short-term safety (follow-up of 30 or 60 days) in 86,000 children, 12 months to 12 years of age and in 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-Marketing Experience

The following additional side 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: Necrotising retinitis (reported only in immunocompromised individuals)

Gastrointestinal Disorders: Nausea; vomiting

Haemic and Lymphatic System: Aplastic anaemia; thrombocytopenia (including idiopathic thrombocytopenic purpura (ITP)); lymphadenopathy

Infections and Infestations: Varicella (vaccine strain)

Nervous/Psychiatric: Encephalitis[†]; cerebrovascular accident; Guillain-Barre syndrome; transverse myelitis; Bell's palsy; ataxia; paresthesia; aseptic meningitis; meningitis[†]; irritability; dizziness; febrile & non-febrile seizures.

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

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

[†]Cases caused by wild-type varicella or vaccine strain varicella have been reported in immunocompromised or immunocompetent individuals.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are no data with regard to overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Epidemiology

Varicella (chicken pox) is a highly communicable disease in children, adolescents, and adults

caused by the varicella-zoster virus. The disease usually consists of 300 to 500 maculopapular and/or vesicular lesions accompanied by a fever (oral temperature $\geq 37^{\circ}\text{C}$) in up to 70% of individuals. Over the period 1993-94 to 1996-97, there has been an average of 73 hospitalizations per month with a principal diagnosis of varicella. Between 1991 and 1996, there was a total of 36 deaths from varicella in Australia. Varicella hospitalization and deaths occur across all ages. 59% of hospitalizations and 39% of deaths from varicella were of children under 15 years (in the years with data available). The hospitalization rate for varicella in children has remained consistently over 11 per 100,000 between 1993-94 and 1996-97. Death rates from varicella for children have ranged between 0.05 and 0.08 per 100,000 during the period 1991 to 1996. Although it is generally a benign, self-limiting disease, varicella may be associated with serious complications (e.g. bacterial superinfection, pneumonia, encephalitis, Reye Syndrome) and/or death.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Clinical trials

Evaluation of Clinical Efficacy Afforded by VARIVAX[®]

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

Clinical Data in Children

One Dose Regimen in Children

In combined clinical trials of varicella vaccine (Oka/Merck) at doses ranging from 1,000-17,000 PFU, the majority of subjects who received varicella vaccine (Oka/Merck) and were exposed to wild-type virus were either completely protected from chickenpox or developed a milder form (for clinical description see below) of the disease. The protective efficacy of varicella vaccine (Oka/Merck) was evaluated in three different ways: 1) by comparing chickenpox rates in vaccinees versus historical controls, 2) by assessment of protection from disease following household exposure, and 3) by a placebo-controlled, double-blind clinical trial.

Although no placebo-controlled trial was carried out with VARIVAX (Refrigerated) the current formulation with urea stabiliser, a placebo-controlled trial was conducted using a formulation containing 17,000 PFU per dose. In this trial, a single dose of varicella vaccine (Oka/Merck) protected 95 to 100% of children against chickenpox over a 2-year period. The study enrolled healthy individuals 1 to 14 years of age (n=491 vaccine, n=465 placebo). In the first year, 8.5% of placebo recipients contracted chickenpox, while no vaccine recipient did, for a calculated protection rate of 100% during the first varicella season. In the second year, when only a subset of individuals agreed to remain in the blinded study (n=169 vaccine, n=163 placebo), 95% protective efficacy was calculated for the vaccine group as compared with placebo.

In early clinical trials with an earlier formulation, a total of 4142 children received 1000 -1625 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been followed for up to six years post single-dose vaccination. In this group there was considerable variation in chickenpox rates among studies and study sites, and much of the reported data were acquired by passive follow-up. It was observed that 2.9 - 3.9% of vaccinees per year reported chickenpox (called breakthrough cases). This represents an approximate 60% (53-68%) decrease from the total number of cases expected based on attack rates in children aged 1-9

over this same period (8.3-9.1%). In those who developed breakthrough chickenpox postvaccination, the majority experienced mild disease (median number of lesions <50). In one study, a total of 47% (27/58) of breakthrough cases had <50 lesions compared with 8% (7/92) in unvaccinated individuals, and 7% (4/58) of breakthrough cases had ≥ 300 lesions compared with 50% (46/92) in unvaccinated individuals. In studies of vaccinated children who contracted chickenpox after a household exposure 54% (22/41) of the cases reported <50 lesions, while one individual [2.4% (1/41)] reported lesions and a fever.

In later clinical trials with an earlier vaccine formulation, a total of 1164 children received 2990-9000 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been followed up 4 years post single-dose vaccination. It was observed that 0.6-1.5% of vaccinees per year reported breakthrough chickenpox for up to 4 years post single-dose vaccination. This represents an approximate 87% (range 82-93%) decrease from the total number of cases expected based on attack rates in children aged 1-9 over this same period (8.3-9.1%). In those who developed breakthrough chickenpox postvaccination, the majority experienced mild disease. Studies in vaccinees examining chickenpox breakthrough rates over 4 years showed the lowest rates (0.6-0.9%) in the first two years postvaccination, with somewhat higher but stable rates (1.5%) in the third year through fourth year. The severity of reported breakthrough chickenpox, as measured by number of lesions and maximum temperature, appeared not to increase with time since vaccination.

Among a subset of vaccinees who were actively followed, 247 were exposed to an individual with chickenpox in a household setting. There were no reports of breakthrough chickenpox in 83% of exposed children; 17% reported a mild form of chickenpox. This represents a 81% reduction in the expected number of cases when compared to the historical rate of varicella following household exposure to chickenpox of 87% in unvaccinated individuals.

There are an insufficient number of breakthrough chickenpox cases in vaccinated children to assess the rate of protection of varicella vaccine (Oka/Merck) against the serious complications of chickenpox (e.g., encephalitis, hepatitis, pneumonia).

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).

Clinical Data in Adolescents and Adults

Although no placebo-controlled trial was carried out in adolescents and adults with VARIVAX Refrigerated, efficacy was determined by evaluation of protection when vaccinees received 2 doses of an earlier formulation of varicella vaccine (Oka/Merck), 4 or 8 weeks apart. Vaccinees were subsequently exposed to chickenpox in a household setting. In up to four years of active follow-up, 14 of 69 (20%) vaccinees reported breakthrough chickenpox following household exposure; of the 14 cases, 9 (64%) reported <50 lesions, and the remaining 5 reported 50 to 75 lesions.

In combined clinical studies of adolescents and adults (n=1017) who received two doses of an earlier varicella vaccine (Oka/Merck) formulation, and later developed breakthrough chickenpox

and reported numbers of lesions (48 of 1017), 30 of 48 (63%) reported <50 lesions, 16 of 48 (33%) reported 50-300 lesions, 1 of 48 (2%) reported 300 lesions and an oral temperature above 37.7°C; 1 of 48 (2%) individuals developed breakthrough chickenpox but the number of lesions is unknown.

There are an insufficient number of breakthrough chickenpox cases among vaccinated adolescents and adults to assess the rate of protection of varicella vaccine (Oka/Merck) against the serious complications of chickenpox (e.g., encephalitis, hepatitis, pneumonia) and during the pregnancy (congenital varicella syndrome).

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 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.

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 cutoff 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 postvaccination in 9610 susceptible children 12 months to 12 years of age. Rates of breakthrough disease were significantly lower among children with varicella antibody titres ≥ 5 gpELISA units compared to children with titres < 5 gpELISA units. Titres ≥ 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 ≥ 5 gpELISA units at 6 weeks postvaccination, an approximate correlation of protection) in subjects participating in follow-up studies ranged from 72 to 98%.

Immunogenicity of VARIVAX Refrigerated (6550 PFU per dose, n=320 and 28,400 PFU per dose, n=315) was compared with that of the previously licensed formulation (9189 PFU per dose, n=323) in a double-blind, randomized, multicenter study in US children 12 to 23 months of age, all of whom received M-M-R* II (Measles, Mumps, and Rubella Virus Vaccine Live) concomitantly. The per-protocol analysis included all subjects with prevaccination varicella antibody titres < 1.25 gpELISA units (n=267 to 276 per group); the antibody responses were comparable across the 3 treatment groups, with 6-week postvaccination varicella antibody titres ≥ 5 gpELISA units in 93.3%, 93.8%, and 95.1% of subjects, respectively.

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:

Table 4

	VARIVAX 1-Dose Regimen (N = 1114)	VARIVAX 2-Dose Regimen (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 ≥ 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 multicenter study involving susceptible adolescents and adults 13 years of age and older, two doses of the earlier formulation of varicella vaccine (Oka/Merck) administered four to eight weeks apart induced a seroconversion rate (gpELISA >0.6) 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 multicenter study involving adolescents and adults, two doses of the earlier formulation of varicella vaccine (Oka/Merck) administered eight weeks apart induced a seroconversion rate (gpELISA >0.6) 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 >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% (532/532) at 6 years postvaccination.

Two Dose Regimen in Children

Over 9 years of follow-up, the GMTs (geometric mean titre) and percent of subjects with VZV antibody titres ≥ 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 >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 postvaccination.

The duration of protection from varicella obtained using varicella vaccine (Oka/Merck) in the absence of wild-type boosting is unknown.

Transmission

In the placebo-controlled trial, transmission of vaccine virus was assessed in household settings (during the 8-week postvaccination period) in 416 susceptible placebo recipients who were household contacts of 445 vaccine recipients. Of the 416 placebo recipients, three developed chickenpox and seroconverted, nine reported a varicella-like rash and did not seroconvert, and six had no rash but seroconverted. If vaccine virus transmission occurred, it did so at a very low rate and possibly without recognizable clinical disease in contacts. These cases may represent either wild-type varicella from community contacts or a low incidence of transmission of vaccine virus from vaccinated contacts (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 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.

Herpes Zoster

Overall, 9543 healthy children (12 months to 12 years of age) and 1652 adolescents and adults (13 years of age and older) have been vaccinated with Oka/Merck live attenuated varicella vaccine in clinical trials. Twelve cases of herpes zoster have been reported in children during 84,414 person years of follow-up in clinical trials, resulting in a calculated incidence of at least 14 cases per 100,000 person years. The completeness of this reporting has not been determined. Two cases of herpes zoster have been reported in the adolescent and adult age group during 12,372 person years of follow-up in clinical trials resulting in a calculated incidence of 16 cases per 100,000 person years.

All fourteen cases were mild and without sequelae. Two cultures (one child and one adult) obtained from the vesicles were positive for wild-type varicella zoster virus as confirmed by restriction endonuclease analysis. The long-term effect of varicella vaccine (Oka/Merck) on the incidence of herpes zoster, particularly in those vaccinees exposed to wild-type varicella, is unknown at present.

In children, the reported rate of zoster in vaccine recipients appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella. The incidence of zoster in adults who have had wild-type varicella infection is higher than that in children.

Reye Syndrome

Reye Syndrome has occurred in children and adolescents following wild-type varicella infection, the majority of whom had received salicylates. In clinical studies in healthy children and adolescents in the United States, physicians advised varicella vaccine recipients not to use salicylates for six weeks after vaccination. There were no reports of Reye Syndrome in varicella vaccine recipients during these studies.

Studies with Other Vaccines

In combined clinical studies involving 1107 children 12 to 36 months of age, 680 received varicella vaccine (Oka/Merck) and M-M-R II (Measles, Mumps and Rubella Virus Vaccine Live) concomitantly at separate sites and 427 received the vaccines six weeks apart. Seroconversion rates and antibody levels were comparable between the two groups at approximately six weeks post-vaccination to each of the virus vaccine components. No differences were noted in adverse reactions reported in those who received varicella vaccine (Oka/Merck) concomitantly with M-M-R II at separate sites and those who received varicella vaccine (Oka/Merck) and M-M-R II at different times (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In a clinical study involving 609 children 12 months to 23 months of age, 305 received varicella vaccine (Oka/Merck), M-M-R II (Measles, Mumps and Rubella Virus Vaccine Live), and a combined vaccine of *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis

concomitantly at separate sites and 304 received M-M-R II and the combined vaccine of *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis given concomitantly followed by varicella vaccine (Oka/Merck) 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella and varicella were similar between the two groups. Compared to prevaccination GMTs the six week postvaccination boost in GMTs for *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis was similar between the two groups.

GMTs for all antigens were similar except for varicella which was lower when varicella vaccine (Oka/Merck) was administered concomitantly with M-M-R II and the combined vaccine of *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis but within the range of GMTs seen in previous clinical experience when varicella vaccine (Oka/Merck) was administered alone. At 1 year postvaccinations GMTs for measles, mumps, rubella and *Haemophilus influenzae* type b were similar between the two groups. All three vaccines were well tolerated regardless of whether they were administered concomitantly at separate sites or 6 weeks apart. There were no clinically important differences in reaction rates when the three vaccines were administered concomitantly versus 6 weeks apart.

Varicella vaccine (Oka/Merck) is recommended for subcutaneous administration. However, during clinical trials, some children received varicella vaccine (Oka/Merck) intramuscularly resulting in seroconversion rates similar to those in children who received the vaccine by the subcutaneous route. Persistence of antibody and efficacy in those receiving intramuscular injections have not been defined.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Not applicable

Distribution

Not applicable

Metabolism

Not applicable

Excretion

Not applicable

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mutagenicity

VARIVAX Refrigerated has not been evaluated for its mutagenic potential.

Carcinogenicity

VARIVAX Refrigerated has not been evaluated for its carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

dibasic sodium phosphate
hydrolysed porcine gelatin
monobasic potassium phosphate

monosodium glutamate monohydrate
potassium chloride
sodium chloride
sucrose
urea

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Storage

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).

Immediately upon receipt of the vaccine shipment, the vaccine must be kept in the refrigerator at a temperature of 2°C to 8°C (36°F to 46°F) until ready for use. **THE VACCINE SHOULD NOT BE FROZEN.**

Before reconstitution, VARIVAX Refrigerated has a shelf-life of 24 months when refrigerated at 2°C to 8°C or colder (36°F to 46°F or colder).

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 150 MINUTES (2 ½ HOURS).

The diluent should be stored separately at room temperature (20°C to 25°C, 68°F to 77°F), or in the refrigerator.

Combination packs with the vaccine vial and vial of diluent or pre-filled syringe of diluent: For combination packs with the 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.**

Stability

VARIVAX Refrigerated has a minimum potency level of approximately 1350 PFU 150 minutes (2½ hours) after reconstitution at room temperature (20°C to 25°C, 68°F to 77°F).

6.5 NATURE AND CONTENTS OF CONTAINER

VARIVAX Refrigerated is supplied as:

- (1) a single dose vial of lyophilised vaccine packed with a single vial of sterile diluent.
- (2) a box of ten single-dose vials of lyophilised vaccine.

- (3) Sterile Diluent for Merck Sharp & Dohme Live Virus Vaccines is available in boxes of 10 vials.
- (4) a single dose vial of lyophilised vaccine packed with a single pre-filled syringe of sterile diluent.
- (5) a blister pack consisting of a single dose vial of lyophilised vaccine packed with a pre-filled syringe of sterile diluent.
- (6) a box of ten single dose vials of lyophilised vaccine packed with ten pre-filled syringes of sterile diluent.
- (7) a box of 10 blisters each consisting of a single dose vial of lyophilised vaccine packed with a single pre-filled syringe of sterile diluent

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not applicable

CAS number

Not applicable

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road,
Macquarie Park NSW 2113
www.msd-australia.com.au

NAME AND ADDRESS OF DISTRIBUTOR

bioCSL Pty Ltd
63 Poplar Road
Parkville VIC 3052

9 DATE OF FIRST APPROVAL

23 December 2002.

10 DATE OF REVISION

10 August 2018.

Summary table of changes

Section changed	Summary of new information
All	Reformatting of PI according to updated TGA PI form (January 2018)
4.8	The term “meningitis” was added based on post-marketing reports. Additional clarifying text regarding immunocompromised or immunocompetent individuals was added.