AUSTRALIAN PRODUCT INFORMATION – VARIVAX ® Refrigerated Varicella virus vaccine live (live varicella vaccine)

1 NAME OF THE MEDICINE

live varicella vaccine

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 Research Laboratories of Merck Sharp & Dohme LLC, Rahway, NJ 07065, USA in human diploid cell cultures (MRC-5) that were free of adventitious agents.

VARIVAX Refrigerated, when reconstituted as directed, is a sterile preparation for intramuscular (IM) or subcutaneous (SC) 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 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

FOR INTRAMUSCULAR OR 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 intramuscularly or subcutaneously. A second dose of VARIVAX administered at least 3 months later is recommended to ensure optimal protection against varicella (see Section 5 PHARMACOLOGICAL PROPERTIES).

Adolescents and adults 13 years of age and older should receive a 0.5 mL dose administered intramuscularly or 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 vaccine should be administered subcutaneously in patients with thrombocytopenia or any coagulation disorder.

Vial of diluent
To reconstitute the vaccine, first withdraw the entire volume 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 entire volume of reconstituted vaccine intramuscularly or 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 volume of diluent in the pre-filled syringe into the vial of lyophilised vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the entire volume of reconstituted vaccine intramuscularly or 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, 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 discolouration 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.

Further information can be found in the Australian Immunisation Handbook.

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). Further information can be found in the Australian Immunisation Handbook.

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 varicella vaccine virus (Oka/Merck) resulting in varicella infection including disseminated disease may occur rarely between vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella including healthy as well as high-risk individuals.

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 varicella or laboratory evidence of prior infection
- newborn infants of mothers without documented history of varicella or laboratory evidence of prior infection

Encephalitis
Encephalitis has been reported during post-marketing use of live attenuated varicella vaccines. In a few cases fatal outcomes have been observed, especially in patients who were immunocompromised (see section 4.3 CONTRAINDICATIONS). Vaccinees/parents should be instructed to seek prompt medical attention if they/their child experience, after vaccination, symptoms suggestive of encephalitis such as loss or reduced levels of consciousness, convulsions or ataxia accompanied by fever and headache.

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), diphtheria and tetanus toxoids and pertussis vaccine adsorbed and *Haemophilus influenzae* type b conjugate combined vaccine, or *Haemophilus influenzae* type b Conjugate (Meningococcal Protein

Conjugate) and Hepatitis B (Recombinant) combined vaccine. If VARIVAX Refrigerated is not given concomitantly with M-M-R II, a 1-month interval between the 2 live virus vaccines should be observed. 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. If VARIVAX Refrigerated 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 Refrigerated can be administered concomitantly with DTaP (diphtheria, tetanus, acellular pertussis) and PedvaxHIB* [*Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate)] 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 subcutaneously to over 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

* Not currently registered in Australia

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 1 to 12 Years of Age
0 to 42 Days After Receipt of a Single Dose of Varicella Vaccine (Oka/Merck)

Reaction	N	% Experiencing Reaction	Peak Occurrence in Post-vaccination Days
Fever ≥39°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 (generalised) Median number of lesions	8913	3.8% 5	5-26

In addition, the most frequently (≥1%) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, cough, irritability, fatigue, disturbed sleep, diarrhoea, loss of appetite, vomiting, otitis, headache, malaise, abdominal pain, other rash, nausea, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions (including allergic rash, hives), stiff neck, arthralgia, 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 refrigerator-stable varicella vaccine (Oka/Merck) (n=635) was compared with that of the licensed frozen formulation of varicella vaccine (Oka/Merck) (n=323) for 42 days post-vaccination 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 ≥ 10% of subjects in one or more treatment groups, irrespective of causal relationship to vaccination) were: fever ≥ 38.9 °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 1 to 12 Years of Age
0 to 42 Days After Receipt of Varicella Vaccine (Oka/Merck)

Reaction	N	Post dose 1 (n=1102)	N	Post dose 2 (n=1022)
Fever ≥ 38.9°C	1077	14.3%	975	10.5%
Injection-site complaints (soreness, erythema, swelling, varicella-like rash, pruritus, ecchymosis, haematoma, 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 After Receipt of Varicella Vaccine (Oka/Merck)

Reaction	N	Post Dose 1	Peak Occurrence in Post-vaccination Days	N	Post Dose 2	Peak Occurrence in Post-vaccination Days
Fever ≥37.7°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)	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 (≥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, diarrhoea, stiff neck, lymphadenopathy, chills, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, lower respiratory illness, allergic reactions (including allergic rash, hives), and dizziness.

Post-Marketing 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-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; syncope.

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 cellulitis; herpes zoster†.

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

* See description of selected adverse reactions.

In a clinical trial, 752 children received VARIVAX, either intramuscularly or subcutaneously. The general safety profile of either administration routes were comparable, although injection-site reactions were less frequent in the IM group (20.9%) compared with the SC group (34.3%).

Description of selected adverse reactions

Complications associated with varicella
Complications of varicella from vaccine strain, including herpes zoster and disseminated disease such as aseptic meningitis and encephalitis have been reported in immunocompromised and immunocompetent individuals. A few cases of encephalitis with a fatal outcome have been observed following vaccination with live attenuated varicella vaccines,

especially in immunocompromised people (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 ≥37°C) in up to 70% of individuals. Over the period 1993-94 to 1996-97, there has been an average of 73 hospitalisations per month with a principal diagnosis of varicella. Between 1991 and 1996, there was a total of 36 deaths from varicella in Australia. Varicella hospitalisation and deaths occur across all ages. 59% of hospitalisations and 39% of deaths from varicella were of children under 15 years (in the years with data available). The hospitalisation 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 varicella 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 to 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 varicella or developed a milder

form (for clinical description see below) of the disease.

The protective efficacy of varicella vaccine (Oka/Merck) administered subcutaneously was evaluated in three different ways: 1) by comparing varicella rates over 7 to 9 years in vaccinees versus historical controls (efficacy 83 to 94%); 2) by assessment of protection from disease following household exposure over 7 to 9 years (efficacy 81 to 88%); and 3) by a placebo-controlled, double-blind clinical trial over 2 years (efficacy 95 to 100%).

Although no placebo-controlled trial was carried out with VARIVAX (Refrigerated) using the current formulation of the vaccine, 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 varicella over a two-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 varicella, 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 4240 children 1 to 12 years of age received 1000 to 1625 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been followed for up to 9 years post single-dose vaccination. In this group, there was considerable variation in varicella rates among studies and study sites, and much of the reported data were acquired by passive follow-up. It was observed that 0.3 to 3.8% of vaccinees per year reported varicella (called breakthrough cases). This represents an approximate 83% (95% confidence interval [CI], 82%, 84%) decrease from the age-adjusted expected incidence rates in susceptible subjects over this same period. In those who developed breakthrough varicella post-vaccination, the majority experienced mild disease (median of the maximum 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.

Among a subset of vaccinees who were actively followed in these early trials for up to 9 years post-vaccination, 179 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 84% (150/179) of exposed children, while 16% (29/179) reported a mild form of varicella (38% [11/29] of the cases with a maximum total number of <50 lesions; no individuals with >300 lesions). This represents an 81% reduction in the expected number of varicella cases utilizing the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

In later clinical trials with an earlier vaccine formulation, a total of 1114 children 1 to 12 years of age received 2900 to 9000 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been actively followed for up to 10 years post single-dose vaccination. It was observed that 0.2 to 2.3% of vaccinees per year reported breakthrough varicella for up to 10 years post single-dose vaccination. This represents an estimated efficacy of 94% (95% CI, 93%, 96%), compared with the age-adjusted expected incidence rates in susceptible subjects over the same period. In those who developed breakthrough varicella post-vaccination, the majority experienced mild disease with the median of the maximum total number of lesions <50. The severity of reported breakthrough varicella, 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 in these later trials for up to 10 years post-vaccination, 95 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella in 92% (87/95) of exposed children; while 8% (8/95) reported a mild form of varicella (maximum total number of

lesions <50; observed range, 10 to 34). This represents an estimated efficacy of 90% (95% CI, 82%, 96%) based on the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

Among 9202 children ≤12 years of age who received 1 injection of varicella vaccine (Oka/Merck), there were 1149 cases of breakthrough varicella (occurring more than 6 weeks post-vaccination) of which 20 (1.7%) were classified as severe (≥300 lesions and a temperature ≥37.8°C oral). Compared with the proportion of severe cases (36%) from wild-type varicella infection in unvaccinated historical controls, this represents a 95% relative reduction in the proportion of severe cases among recipients of varicella vaccine who developed breakthrough varicella.

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 randomised to receive either 1 dose of varicella vaccine (Oka/Merck) (n=1114) or 2 doses of varicella vaccine (Oka/Merck) (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 varicella-zoster vaccine (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 post-vaccination 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).

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

Clinical Data in Adolescents and Adults

Although no placebo-controlled trial was carried out in adolescents and adults, the protective efficacy of varicella vaccine (Oka/Merck) was calculated by evaluation of protection when vaccinees received 2 doses of an earlier formulation of varicella vaccine (Oka/Merck) 4 or 8 weeks apart and were subsequently exposed to varicella in a household setting over 6 to 7 years. In earlier clinical trials with up to 6 years of follow-up, 13 of the 76 individuals (17%) who had household exposure to varicella, developed varicella. All of the varicella cases that were reported were generally mild with a median of 37 lesions (range 8 to 75). In later clinical trials with up to 7 years of follow-up, none of 19 individuals (0%) who had household exposure developed varicella.

The attack rate of unvaccinated adults exposed to a single contact in a household has not been previously studied. If the attack rate of 87% following household exposure in susceptible children holds true for susceptible adolescents and adults, the estimated efficacy of the vaccine in the prevention of any varicella disease would range from 80 to 100%.

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

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 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 ≥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 post-vaccination, an approximate correlation of protection) in subjects participating in follow-up studies ranged from 72 to 98%.

Immunogenicity of refrigerator-stable varicella vaccine (Oka/Merck) (6550 PFU per dose, n=320 and 28,400 PFU per dose, n=315), was compared with that of the licensed frozen formulation (9189 PFU per dose, n=323) in a double-blind, randomised, 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, 2216 healthy children 12 months to 12 years of age received either 1 dose or two doses of varicella vaccine (Oka/Merck) administered subcutaneously 3 months apart. The immunogenicity results are shown in the following table:

Table 4
Summary of VZV Antibody Responses at 6 Weeks Post dose 1 and 6 Weeks Post dose 2 in Initially Seronegative Children 12 Months to 12 Years of Age (Vaccinations 3 Months Apart)

	Varicella Vaccine (Oka/Merck)1-Dose Regimen (N = 1114)	Varicella Vaccine (Oka/Merck)2-Dose Regimen (3 Months Apart) (N = 1102)	
	6 Weeks Post-vaccination (n=892)	6 Weeks Post dose 1 (n=851)	6 Weeks Post dose 2 (n=769)
Seroconversion Rate	98.9%	99.5%	99.9%
Percent with VZV Antibody Titre ≥5 gpELISA units/mL	84.9%	87.3%	99.5%
Geometric Mean Titres in gpELISA units/mL (95% CI)	12.0 (11.2, 12.8)	12.8 (11.9, 13.7)	141.5 (132.3, 151.3)

N = Number of subjects vaccinated.
n = Number of subjects included in immunogenicity analysis.

The results from this study and other studies in which a second dose of varicella vaccine (Oka/Merck) was administered 3 to 6 years after the initial dose demonstrate significant boosting of the VZV antibodies 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 subcutaneously four to eight weeks apart induced a seroconversion rate (gpELISA ≥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 multicenter study involving adolescents and adults, two doses of the earlier formulation of varicella vaccine (Oka/Merck) administered subcutaneously eight weeks apart induced a seroconversion rate (gpELISA ≥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 ≥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 ≥5 gpELISA units/mL in the 2-dose recipients were higher than those in the 1-dose recipients administered subcutaneously 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 VARIVAX subcutaneously, 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 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.

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

Transmission

In the placebo-controlled trial, transmission of vaccine virus was assessed in household settings

(during the 8-week post-vaccination period) in 416 susceptible placebo recipients who were household contacts of 445 vaccine recipients. Of the 416 placebo recipients, three developed varicella 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. Post-marketing experience suggests that transmission of varicella vaccine virus (Oka/Merck) resulting in varicella infection including disseminated disease may occur rarely between vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella including healthy as well as high-risk individuals (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Transmission).

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 varicella vaccine (Oka/Merck) 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 14 cases of herpes zoster were mild and no sequelae were reported. 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 children received varicella vaccine (Oka/Merck) and M-M-R II (Measles, Mumps and Rubella Virus Vaccine Live) administered subcutaneously and 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 *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis combined vaccine

concomitantly at separate sites and 304 received M-M-R II and *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis combined vaccine given concomitantly followed by varicella vaccine (Oka/Merck) 6 weeks later. At six weeks post-vaccination, seroconversion rates for measles, mumps, rubella and varicella were similar between the two groups. Compared to prevaccination GMTs the six week post-vaccination 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 *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis combined vaccine but within the range of GMTs seen in previous clinical experience when varicella vaccine (Oka/Merck) was administered alone. At 1 year post-vaccination, GMTs for measles, mumps, rubella, varicella 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.

In a clinical study involving 822 children 12 to 15 months of age, 410 received *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine, M-M-R II, and varicella vaccine (Oka/Merck) concomitantly at separate sites, and 412 received *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine followed by M-M-R II and varicella vaccine (Oka/Merck) given concomitantly at separate sites, 6 weeks later. In this study VARIVAX was administered subcutaneously. At 6 weeks post-vaccination, the immune responses for the subjects who received the concomitant injections of *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine, M-M-R II, and varicella vaccine (Oka/Merck) were similar to those of the subjects who received *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine followed 6 weeks later by M-M-R II and varicella vaccine (Oka/Merck) with respect to all antigens administered. All 3 vaccines were generally 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 3 vaccines were administered concomitantly versus 6 weeks apart.

VARIVAX (Refrigerated) is recommended for intramuscular or subcutaneous administration. 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
*contains sulfites

Diluent
Water for injections

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
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).

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).

Prefilled syringe of diluent
The diluent should be stored separately at room temperature (20°C to 25°C, 68°F to 77°F), or in the refrigerator. **Do not freeze the diluent.**

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 a single-dose vial of lyophilised vaccine packed with a single vial of sterile diluent.

(3) a box of 5 single-dose vial of lyophilised vaccine packed with 5 single vials of sterile diluent.

(4) a box of 10 single-dose vials of lyophilised vaccine.

(5) Sterile Diluent for Merck Sharp & Dohme Live Virus Vaccines is available in boxes of 10 vials.

(6) a box of 1 blister pack consisting of a single dose vial of lyophilised vaccine packed with a pre-filled syringe of sterile diluent.

(7) a box of 10 blisters packs each consisting of a single dose vial of lyophilised vaccine packed with a single pre-filled syringe of sterile diluent.

Not all presentations and packs sizes may be supplied.

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

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road,
Macquarie Park NSW 2113
http://www.msd-australia.com.au
Tel: (+61) 02 8988 8000

9 DATE OF FIRST APPROVAL

23 December 2002

10 DATE OF REVISION

13 March 2026

Summary table of changes

Section changed	Summary of new information
4.4, 4.8	Updated to better describe the severity of the known risk of encephalitis
4.3, 4.4	Added statement “Further information can be found in the Australian Immunisation Handbook.”

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