

PRODUCT MONOGRAPH

VARIVAX® III

(varicella virus vaccine, live, attenuated [Oka/Merck])

Lyophilized powder for injection

Active immunizing agent against varicella

Merck Canada Inc.
16750 route Transcanadienne
Kirkland, QC H9H 4M7
Canada
<http://www.merck.ca>

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VARIVAX® III

(varicella virus vaccine, live, attenuated [Oka/Merck])

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Lyophilized powder reconstituted for injection. Each 0.5 mL dose contains a minimum of 1350 PFU (plaque-forming units) of Oka/Merck varicella virus*	Hydrolyzed gelatine and neomycin <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

* Minimum potency remaining at expiry 90 minutes after reconstitution and storage at room temperature.

DESCRIPTION

VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) is a live, attenuated virus vaccine (a lyophilized preparation of the Oka/Merck strain of varicella).

INDICATIONS AND CLINICAL USE

VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) is indicated for vaccination against varicella in individuals 12 months of age and older.

Revaccination

The duration of protection of VARIVAX® III is unknown at present and the need for booster doses is not defined. However, a boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella as well as following a booster dose of varicella vaccine (Oka/Merck) administered four to six years postvaccination.

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. The National Advisory Committee on Immunization (NACI) does not recommend any booster dose(s) after the age-appropriate primary immunization (see DOSAGE AND ADMINISTRATION).¹

Vaccination with VARIVAX[®] III may not result in protection of all healthy, susceptible children, adolescents, and adults (see CLINICAL TRIALS).

CONTRAINDICATIONS

VARIVAX[®] III (varicella virus vaccine, live, attenuated [Oka/Merck]) should not be administered to:

- Individuals with a history of hypersensitivity to any component of the vaccine, including gelatin.
- Individuals with 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[†] (including high-dose corticosteroids); however, VARIVAX[®] III is not contraindicated for use with topical corticosteroids or low-dose corticosteroids, as are commonly used for asthma prophylaxis. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Vaccination with live attenuated varicella vaccine can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids.
- Individuals with primary and acquired immunodeficiency states, including immunosuppression in association with AIDS or other clinical manifestations of infection with human immunodeficiency virus, except immunosuppression in asymptomatic children with CD4 T-lymphocyte percentages $\geq 25\%$.
- Individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.
- Individuals with active untreated tuberculosis.
- Individuals with any active febrile illness with fever $> 38.5^{\circ}\text{C}$; however, low-grade fever itself is not a contraindication to vaccination.

[†]The National Advisory Committee on Immunization states that there is no additional or undue risk in vaccinating the following persons: Patients with nephrotic syndrome or those undergoing hemodialysis and peritoneal dialysis if they are not on immunosuppressive medication; Patients on low-dose steroid therapy (e.g., < 2 mg prednisone/kg/day to a maximum of 20 mg/day for < 2 weeks); Patients on inhaled or topical steroids.¹

- Women who are pregnant; 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 WARNINGS AND PRECAUTIONS, Pregnant Women).

WARNINGS AND PRECAUTIONS

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX[®] III (varicella virus vaccine, live, attenuated [Oka/Merck]) as Reye's syndrome has been reported following the use of salicylates during wild-type varicella infection.

General

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactoid reaction occur.²

The duration of protection from varicella infection after vaccination with VARIVAX[®] III is unknown.

The United States Advisory Committee on Immunization Practices (ACIP)³ and NACI¹ recommend the vaccine for use in susceptible persons following exposure to varicella (if used within 3 days, and possibly up to 5 days of exposure).

There is an insufficient number of breakthrough chickenpox cases among vaccinated children, adolescents and adults to assess the rate of protection of VARIVAX[®] III against the serious complications of chickenpox (e.g., encephalitis, hepatitis, pneumonia) and during pregnancy (congenital varicella syndrome).

Transmission

Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts.

Transmission of vaccine virus from vaccinees who do not develop a varicella-like rash has also been reported.

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

- immunocompromised individuals

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

Special Populations

Pregnant Women:

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

A unique Oka/Merck Pregnancy Registry has been in place since 1995. Reporting to the Registry was voluntary. In the first 10 years of the Pregnancy Registry for varicella vaccine (Oka/Merck), of 138 seronegative women and 440 women of unknown serostatus who received varicella vaccine during pregnancy or within 3 months before pregnancy, none had newborns with abnormalities compatible with congenital varicella syndrome. In case of inadvertent use of the Oka/Merck varicella vaccine in a pregnant woman, please contact Merck Canada Inc.

Nursing Women:

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[®] III is administered to a nursing woman.

Pediatrics:

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

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another vaccine. Adverse drug reaction information from clinical trials is useful for identifying vaccine-related adverse events and for approximating rates.

In clinical trials, varicella vaccine (Oka/Merck) was administered to approximately 17,000 healthy children, adolescents, and adults. Varicella vaccine (Oka/Merck) was generally well tolerated.^{4,5}

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.⁶

Children 1 to 12 Years of Age

In clinical trials involving approximately 8900 healthy children monitored for up to 42 days after a single dose of varicella vaccine (Oka/Merck) the frequency of fever, injection-site complaints, or rashes were reported in Table 1.

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

Reaction	N	Postdose 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)	8913	3.4%	8–19
Median number of lesions		2	
Varicella-like rash (generalized)	8913	3.8%	5–26
Median number of lesions		5	

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

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

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

Adolescents and Adults 13 Years of Age and Older

In clinical trials involving approximately 1600 healthy adolescents and adults, the majority of whom received two doses of varicella vaccine (Oka/Merck) and were monitored for up to 42 days after any dose, the frequency of fever, injection-site complaints, or rashes were reported in Table 2.

Table 2
Fever, Local Reactions or Rashes (%) in Adolescents and Adults 0 to 42 Days Postvaccination

Reaction	N	Postdose 1	Peak Occurrence in Postvaccination Days	N	Postdose 2	Peak Occurrence in Postvaccination 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)	1606	3.1%	6–20	955	1.0%	0–6
Median number of lesions		2			2	
Varicella-like rash (generalized)	1606	5.5%	7–21	955	0.9%	0–23
Median number of lesions		5			5.5	

In addition, the most frequently ($\geq 1\%$) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, irritability/nervousness, diarrhea, 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 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.⁷

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

Post-Market Adverse Drug Reactions

Since the vaccine has been marketed, the following additional adverse reactions have been reported regardless of causality:

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

Gastrointestinal Disorders: nausea; vomiting.

Hemic and Lymphatic System: Aplastic anemia; thrombocytopenia (including idiopathic thrombocytopenic purpura (ITP)); lymphadenopathy.

Infections and Infestations: Varicella (vaccine strain).

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

Respiratory: Pharyngitis; pneumonia/pneumonitis.

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

DRUG INTERACTIONS

Drug-Drug 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[®] III (varicella virus vaccine, live, attenuated [Oka/Merck]), any immune globulin including VZIG should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination.

Results from clinical studies indicate that varicella vaccine (Oka/Merck) can be administered concomitantly with M-M-R[®] II (measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.) or Tetramune (diphtheria and tetanus toxoids and pertussis vaccine adsorbed and *Haemophilus b* conjugate vaccine). If varicella vaccine (Oka/Merck) is not given concomitantly with M-M-R[®] II, a one month interval between the two live virus vaccines should be observed.¹

Limited data from an experimental product containing varicella vaccine suggest that varicella vaccine (Oka/Merck) can be administered concomitantly with DTaP (diphtheria, tetanus, acellular pertussis) and Liquid PedvaxHIB[®] [*Haemophilus b* conjugate vaccine (meningococcal protein conjugate)] using separate sites and syringes and with OPV (oral poliovirus vaccine).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Pediatrics

Children 12 months to 12 years of age should receive a single 0.5 mL dose administered subcutaneously.

Adolescents/Adults

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

Administration

FOR SUBCUTANEOUS ADMINISTRATION ONLY.

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

Do not inject intradermally, intravenously, or intramuscularly.

VARIVAX[®] III (varicella virus vaccine, live, attenuated [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.⁸ Persistence of antibody and efficacy in those receiving intramuscular injections have not been defined.

Reconstitution

To reconstitute the vaccine, use only the diluent supplied (Sterile Diluent for Merck Sharp & Dohme Corp., live, attenuated, virus vaccines), since it is free of preservatives or other anti-viral substances that might inactivate the vaccine virus.

CAUTION: A sterile syringe free of preservatives, antiseptics and detergents should be used for each injection and/or reconstitution of VARIVAX[®] III 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, 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 lyophilized vaccine and gently agitate to mix thoroughly.

Prior to administration: Inspect the reconstituted solution for particulate matter and discoloration, whenever solution and container permit. VARIVAX[®] III, when reconstituted, is a clear, colourless to pale yellow liquid.

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. **TO MINIMIZE LOSS OF POTENCY, IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION. DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 90 MINUTES. DO NOT REFREEZE RECONSTITUTED VACCINE.**

OVERDOSAGE

There are no data with regard to overdose.

For management of a suspected overdose, contact your regional Poison Control Centre.
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ACTION AND CLINICAL PHARMACOLOGY

Varicella

Varicella is a highly communicable disease in children, adolescents, and adults caused by the varicella-zoster virus (VZV). The disease usually consists of 300 to 500 maculopapular and/or vesicular lesions accompanied by a fever [oral temperature $\geq 37.7^{\circ}\text{C}$] in up to 70% of individuals.^{9,10} In Canada, it is estimated that about 350,000 cases occur each year and that 1871 of them will require hospitalization (complicated cases).¹¹ Approximately 3.5 million cases of varicella occurred annually from 1980–1994 in the United States with the peak incidence occurring in children five to nine years of age.¹² The incidence rate of chickenpox was 8.3–9.1% per year in children one to nine years of age.⁶ The attack rate of wild-type varicella following household exposure among healthy susceptible children was shown to be 87%. Although it is generally a benign, self-limiting disease, varicella may be associated with serious complications (e.g., bacterial superinfection, pneumonia, encephalitis, Reye's syndrome), and/or death. In Canada, during 1994 and 1995, a total of 24 deaths were reported to be caused by chickenpox.¹³

Varicella-zoster virus infection is associated with a 58-fold (95% confidence interval [CI]: 40, 85) increased risk of acquiring invasive Group A Streptococcal (GAS) disease in children. Children with invasive GAS disease and recent chickenpox were more likely to have necrotizing fasciitis (NF) (RR: 6.3; 95% CI: 1.8, 22.3).¹⁴

STORAGE AND STABILITY

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature between -50°C and $+8^{\circ}\text{C}$. Use of dry ice may subject VARIVAX[®] III to temperatures colder than -50°C .

Before reconstitution, VARIVAX[®] III (varicella virus vaccine, live, attenuated [Oka/Merck]) has a shelf-life of 24 months and should be stored refrigerated at a

temperature of 2°C to 8°C. The vaccine may also be stored in a freezer at temperatures above -50°C; if subsequently transferred to a refrigerator, the vaccine may be placed back in the freezer.

VARIVAX[®] III can be administered provided the total (cumulative multiple excursions) time out of refrigeration (prior to reconstitution, at temperatures between 8°C and 25°C) does not exceed 6 hours. These are not, however, recommendations for storage.

Do not use past expiry date on the label. Protect from light.

The vial of diluent should be stored separately at room temperature (20°C to 25°C) or in the refrigerator (2°C to 8°C). **Do not freeze the diluent.**

All vaccines must be discarded after the expiration date.

VARIVAX[®] III has a minimum potency level of approximately 1350 PFU 90 minutes after reconstitution at room temperature (20°C to 25°C). **Discard if reconstituted vaccine is not used within 90 minutes. Do not refreeze reconstituted vaccine.**

For additional information regarding stability under conditions other than recommended, call at 1-800-567-2594.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

VARIVAX[®] III (varicella virus vaccine, live, attenuated [Oka/Merck]) is supplied as a sterile, lyophilized white powder in a single-dose vial.

The diluent (Sterile Diluent for Merck Sharp & Dohme Corp., live, attenuated, virus vaccines) is a sterile, clear, colourless fluid supplied separately in a single-dose vial.

After reconstitution, VARIVAX[®] III is a clear, colourless to pale yellow liquid.

Composition

When reconstituted as directed, each single dose (0.5 mL) contains:

Active Ingredients

Varicella virus, Oka/Merck strain (live, attenuated) ≥ 1350 PFU*

*Minimum potency remaining at expiry 90 minutes after reconstitution and storage at room temperature.

Other Ingredients

<i>Excipients</i>	18 mg
Sucrose	8.9 mg
Hydrolyzed gelatin	3.6 mg
Urea	2.3 mg
Sodium chloride	0.36 mg
Monosodium L-glutamate	0.33 mg
Sodium phosphate dibasic	57 µg
Potassium phosphate monobasic	57 µg
Potassium chloride	to volume
Water for injection	

The product contains no preservative.

The diluent is sterile water for injection.

Manufacturing Process Residuals

The product also contains residual components of MRC-5 cells including DNA and protein, and trace quantities of neomycin and fetal bovine serum from MRC-5 culture media.

Packaging

VARIVAX[®] III is supplied in 3 mL single-dose Type I glass vials. Each vial contains one dose of lyophilized vaccine (approximately 0.5 mL when reconstituted as directed).

The diluent (0.7 mL) is supplied separately in 3 mL single-dose Type I glass vials.

The container closure systems of VARIVAX[®] III and the diluent are free of latex.

VARIVAX[®] III is available in packages of 1 and 10 single-dose vials.

The diluent is also available in packages of 1 and 10 single-dose vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Varicella virus vaccine, live, attenuated [Oka/Merck]

Product Characteristics

VARIVAX[®] III (varicella virus vaccine, live, attenuated [Oka/Merck]) is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella virus. When reconstituted as directed, it 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 90 minutes. The product contains no preservative.

CLINICAL TRIALS

Clinical Data in Children

In combined clinical trials of varicella virus vaccine, live, attenuated (Oka/Merck), hereafter referred to as varicella vaccine (Oka/Merck), at doses ranging from 1000–17,000 PFU, the majority of subjects who received the vaccine 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 a placebo-controlled, double-blind clinical trial over 2 years (efficacy 95 to 100%); 2) by comparing chickenpox rates over 7 to 9 years in vaccinees versus historical controls; and 3) by assessment of protection from disease following household exposure over 7 to 9 years.

Although no placebo-controlled trial was carried out with varicella vaccine (Oka/Merck) using the current formulation of the vaccine, a placebo-controlled trial was conducted using a formulation containing 17,000 PFU per dose.^{6,15} In this trial, a single dose of varicella vaccine (Oka/Merck) protected 95 to 100% of children against chickenpox 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 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 to placebo.

In early clinical trials, a total of 4240 children received 1000 to 1625 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been followed for up to nine 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 0.3 to 3.8% of vaccinees per year reported chickenpox (called breakthrough cases), with an average of 2.5% per year (cumulative event rate of 19.4% by the end of the ninth year). The calculated annual rates in historical control groups, based on one published study¹⁶ are 9.7%, 19.7%, and 11.6% in susceptible subjects who were 1–4, 5–9 and 10–14 years of age, respectively, corresponding to a rate of 14.8% per year in an unvaccinated cohort comparable in age to the vaccinated cohort.⁶ In those who developed breakthrough chickenpox postvaccination, 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.¹⁷

Among a subset of vaccinees who were actively followed in these early trials for up to 9 years postvaccination, 179 individuals had household exposure to chickenpox. There were no reports of breakthrough chickenpox in 84% (150/179) of exposed children while 16% (29/179) reported varicella after household exposure compared with the historical attack rate of 87% (388/447 children with no history of chickenpox) following household exposure to chickenpox in unvaccinated individuals. The historical rate was derived from one published article.¹⁰ In the 29 subjects in whom varicella occurred postvaccination the disease was generally mild with respect to the number of lesions and no individuals had ≥ 300 lesions.

In later clinical trials, a total of 1164 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 7 years post single-dose vaccination. It was observed that 0.2 to 2.3% of vaccinees per year reported chickenpox (called breakthrough cases), with an average of 0.9% per year (cumulative event rate of 6.7% by the end of the seventh year). The calculated annual rates in historical control groups, based on one published study¹⁶ are 9.7%, 19.7%, and 11.6% in susceptible subjects who were 1–4, 5–9, and 10–14 years of age, respectively, corresponding to a rate of 15.3% per year in an unvaccinated cohort comparable in age to the vaccinated cohort.⁶ In those who developed breakthrough chickenpox postvaccination, the majority experienced mild disease with the median of the maximum total number of lesions < 50. 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 in these later trials for up to 7 years postvaccination, 80 individuals were exposed to an unvaccinated individual with wild-type chickenpox in a household setting. There were no reports of breakthrough chickenpox in 90% (72/80) of exposed children, while 10% (8/80) reported varicella after household exposure as compared with the historical attack rate of 87% (388/447 children with no history of chickenpox) following household exposure to chickenpox in unvaccinated individuals. The historical rate was derived from one published article.¹⁰ The reported cases of varicella were mild, with annual median number of lesions (maximum daily total) ranging from 10 to 34.

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 postvaccination) of which 20 (1.7%) were classified as severe (≥ 300 lesions and a temperature $\geq 37.8^\circ\text{C}$ oral). By comparison, in a survey of 150 children 1 to 16 years of age, including 92 cases of varicella in previously unvaccinated children and 58 cases of varicella following vaccination, 36% of those unvaccinated had a severe case.

There is 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).

VARIVAX[®] III 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.

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 varicella vaccine (Oka/Merck) 4 or 8 weeks apart and were subsequently exposed to chickenpox 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 chickenpox, 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 to chickenpox, developed varicella.

There is 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 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.^{4,6,18-22}

Seroconversion as defined by the acquisition of any detectable varicella antibodies (based on assay cut-off that generally corresponds to 0.6 units in the gpELISA, a highly sensitive assay which is not commercially available), was observed in 98% of vaccinees at approximately 4 to 6 weeks postvaccination in 9610 susceptible children 12 months to 12 years of age who received doses ranging from 1000 to 50,000 PFU. The antibody titer determined by gpELISA has been

shown to correlate with levels of neutralizing antibody and can therefore be regarded as a clinically relevant marker of functional immunity. An inverse relationship was established between the varicella antibody titer 6 weeks after vaccination and the risk of breakthrough varicella. It can be regarded as an approximate correlate of protection for individual vaccinees.²³ Rates of breakthrough disease were significantly lower among children with varicella antibody titers ≥ 5 gpELISA units compared to children with titers < 5 gpELISA units. Titers ≥ 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 titers ≥ 5 gpELISA units at 6 weeks postvaccination, an approximate correlate of protection) in subjects participating in follow-up studies ranged from 72 to 98%.

In a multicenter study involving susceptible adolescents and adults 13 years of age and older, two doses of varicella vaccine (Oka/Merck) administered four to eight weeks apart induced a seroconversion rate (gpELISA ≥ 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 varicella vaccine (Oka/Merck) administered 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.

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

Post-immunization Serological Testing

Post-immunization serological testing for immunity is not recommended by NACI, because of the high level of immunity conferred by the vaccine, and because currently available commercial laboratory tests are not sufficiently sensitive to detect vaccine-induced antibodies.¹

Persistence of Immune Response

In those clinical studies involving healthy children who received 1 dose of vaccine, detectable varicella antibodies (gpELISA ≥ 0.6 units) were present in 99.0% (3881/3921) at 1 year, 99.2% (1551/1564) at 2 years, 98.6% (1090/1105) at 3 years, 99.2% (636/641) at 4 years, 97.9% (286/292) at 5 years, 100% (131/131) at 6 years, and 96.4% (27/28) at 7 years postvaccination.

In clinical studies involving healthy adolescents and adults who seroconverted after 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.

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.

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 WARNINGS AND PRECAUTIONS, Transmission).^{6,24} 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 (see WARNINGS AND PRECAUTIONS, 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 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 14 cases were mild and no sequelae were reported. Two cultures (one child and one adult) obtained from 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.¹⁶ The incidence of zoster in adults who have had wild-type varicella infection is higher than that in children.

Reye's Syndrome

Reye's 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's syndrome in varicella vaccine recipients during these studies (see WARNINGS AND PRECAUTIONS).

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 attenuated, Merck Std.) 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 postvaccination 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.

In a clinical study involving 316 children 12 months to 42 months of age, 160 received an investigational vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with booster doses of DTaP (diphtheria, tetanus, acellular pertussis) and OPV (oral poliovirus vaccine) while 156 received M-M-R[®] II concomitantly with booster doses of DTaP and OPV followed by varicella vaccine (Oka/Merck) 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and varicella and the percentage of vaccinees whose titers were boosted for diphtheria, tetanus, pertussis, and polio were comparable between the two groups, but anti-varicella levels were decreased when the investigational vaccine containing varicella was administered concomitantly with DTaP. No clinically significant differences were noted in adverse reactions between the two groups.

In another clinical study involving 306 children 12 to 18 months of age, 151 received an investigational vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with a booster dose of Liquid PedvaxHIB[®] [*Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate)] while 155 received M-M-R[®] II concomitantly with a booster dose of Liquid PedvaxHIB[®] followed by varicella vaccine (Oka/Merck) 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and varicella, and geometric mean titers for Liquid PedvaxHIB[®] were comparable between the two groups, but anti-varicella levels were decreased when the investigational vaccine containing varicella was administered concomitantly with Liquid PedvaxHIB[®]. No clinically significant differences in adverse reactions were seen between the two groups.

In a clinical study involving 609 children 12 months to 23 months of age, 305 received varicella vaccine (Oka/Merck), M-M-R[®] II, and Tetramune (*Haemophilus influenzae* type b, diphtheria, tetanus, and pertussis vaccines) concomitantly at separate sites and 304 received M-M-R[®] II and Tetramune 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 Tetramune but within the range of GMTs seen in previous clinical experience when varicella vaccine (Oka/Merck) was administered alone. At 1 year postvaccination, 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.

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PART III: CONSUMER INFORMATION**VARIVAX® III**

(varicella virus vaccine, live, attenuated [Oka/Merck])

This leaflet is part III of a three-part "Product Monograph" published when VARIVAX® III was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VARIVAX® III. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINEWhat the vaccine is used for:

VARIVAX® III is an injectable live virus vaccine to help prevent chickenpox (varicella). The vaccine can be administered to persons 12 months of age or older.

What it does:

Your doctor has recommended or administered VARIVAX® III to help protect you or your child against chickenpox.

Chickenpox is easily passed from one person to another and occurs in millions of people worldwide each year, most often in children 5 to 9 years of age. Although chickenpox is generally a fairly harmless disease, it may be associated with serious complications (such as bacterial skin infections, pneumonia, inflammation of the brain, Reye's syndrome) and/or rarely death.

When it should not be used:

VARIVAX® III should not be used by anyone who:

- is allergic to any of its ingredients (including gelatin and neomycin). A list of ingredients can be found below
- has a blood disorder or any type of cancer that affects their immune system
- is taking medications to suppress their immune system
- has an immune deficiency, including one as a result of a disease (such as AIDS)
- has active untreated tuberculosis
- has a fever > 38.5°C (> 101.3°F)
- is pregnant (in addition, pregnancy should be avoided for 3 months after vaccination)

What the medicinal ingredient is:

Each 0.5 mL dose contains as active ingredient a minimum of 1350 PFU (plaque-forming units) of live attenuated varicella virus (Oka/Merck strain).

What the important nonmedicinal ingredients are:

Powder: sucrose, hydrolyzed gelatin, urea, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, and trace quantities of neomycin.

Diluent: water for injection.

What dosage forms it comes in:

VARIVAX® III is supplied as a sterile white powder in a single-dose vial.

The diluent for reconstitution is supplied as a sterile, clear, colourless fluid in a single-dose vial.

When reconstituted, VARIVAX® III is a clear, colourless to pale yellow fluid.

WARNINGS AND PRECAUTIONS**What should I tell my doctor before vaccination with VARIVAX® III?**

Tell your doctor about any medical problems you or your child have or have had, and about any allergies (especially to gelatin or neomycin). VARIVAX® III contains gelatin and a trace amount of neomycin as inactive ingredients.

Tell your doctor if there is anyone who comes in close contact with the person being vaccinated who falls into one of the following categories, since these individuals may be at risk of catching chickenpox from the person who was vaccinated:

- individuals with a weakened immune system
- pregnant women who never had chickenpox
- newborn babies whose mothers never had chickenpox.

Use in children

VARIVAX® III can be used in children 12 months of age and older.

Use in pregnancy

VARIVAX® III should not be administered to pregnant women. Women of child-bearing age should take the necessary precautions to avoid pregnancy for 3 months following vaccination.

Use in breast-feeding

Tell your doctor if you are breast-feeding or intend to breast-feed. Your doctor will decide if you should receive VARIVAX® III.

Can I drive or operate machinery following vaccination with VARIVAX® III?

There is no information to suggest that VARIVAX® III affects your ability to drive or operate machinery.

What other important information about VARIVAX® III should I know?

As with other vaccines, VARIVAX® III may not fully protect all those who receive it.

INTERACTIONS WITH THIS VACCINE

Vaccine recipients should avoid salicylates (medications derived from salicylic acid, including aspirin) for 6 weeks after vaccination with VARIVAX[®] III as Reye's syndrome (a serious condition which can affect all your body organs) has been reported following use of salicylates during natural varicella infection.

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

Following vaccination with VARIVAX[®] III, you or your child should not receive any immune globulin, including VZIG, for 2 months thereafter, unless your doctor decides it is necessary.

VARIVAX[®] III can be given at the same time as measles, mumps and rubella vaccine (M-M-R[®] II) and vaccines against *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis (whooping cough). If VARIVAX[®] III is not given at the same time as M-M-R[®] II a 1-month interval between these 2 vaccines should be observed. Your doctor will decide the vaccination schedule.

PROPER USE OF THIS VACCINE

Usual dose:

VARIVAX[®] III is given by subcutaneous injection as follows:

- Children 12 months to 12 years of age should receive a single dose. The dose of the vaccine is the same for everyone.
- Adolescents and adults 13 years of age and older should receive two doses. The second dose should be given 4 to 8 weeks after the first dose.

See your doctor for more details.

Overdose:

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

If you miss a dose, your doctor will decide when to give the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any vaccine may have unintended or undesirable effects, so-called side effects. The most common are injection site complaints such as pain, swelling, itching and redness. Occasionally, fever, irritability, tingling of the skin, shingles, or a chickenpox-like rash on the body or at the injection site may occur.

Other side effects such as nausea, vomiting, and chickenpox have been reported. Some reported side effects were serious, including allergic reactions (in individuals with or without an allergic history); bruising more easily than normal; red or purple, flat, pinhead spots under the skin; severe paleness; difficulty walking; severe skin disorders; and skin infection. Rarely, inflammation of the brain (encephalitis), stroke (cerebrovascular accident), inflammation of the lung (pneumonia/pneumonitis) and seizures with or without a fever have been reported. The relationship of these rare side effects to the vaccine has not been established.

Tell your doctor promptly about any of these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

This is not a complete list of side effects. For any unexpected effects while taking VARIVAX[®] III, contact your doctor or pharmacist.

HOW TO STORE IT

Vial of powder: Store refrigerated at 2°C to 8°C. The vaccine may also be stored in a freezer at temperatures above -50°C; if subsequently transferred to a refrigerator, the vaccine may be placed back in the freezer. Keep the vial in the outer carton in order to protect from light.

Diluent: Store separately from the vaccine vial at room temperature (20°C to 25°C) or in the refrigerator at 2°C to 8°C.

All vaccines must be discarded after the expiration date.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in **your province/territory**.

For the General Public:

Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada.

By toll-free telephone: 1-866-844-0018

By toll-free fax: 1-866-844-5931

By e-mail: caefi@phac-aspc.gc.ca

Web: <http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>

Mail:

The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A 0K9

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594:
- Complete an Adverse Events following Immunization (AEFI) Form and
 - Fax toll-free to 1-800-369-3090, or
 - Mail to: Merck Canada Inc.
Pharmacovigilance
P.O. Box 1005
Pointe-Claire-Dorval, QC H9R 4P8

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada or Merck do not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.merck.ca>

or by contacting the sponsor, Merck Canada Inc.,
at: 1-800-567-2594.

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