

PRODUCT MONOGRAPH

VARIVAX® III

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

Lyophilized Powder for Injection

THERAPEUTIC CLASSIFICATION

Active immunizing agent against varicella

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ACTION AND CLINICAL PHARMACOLOGY

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).

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].^{1,2} In Canada, it is estimated that about 350,000 cases occur each year and that 1871 of them will require hospitalization (complicated cases).³ 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.⁴ The incidence rate of chickenpox was 8.3-9.1% per year in children one to nine years of age.⁵ 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.⁶

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).⁷

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.^{5,8} 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 vaccinee, n=465 placebo). In the first year, 8.5% of placebo recipients contracted chickenpox, while no vaccinee 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 vaccinee, n=163 placebo), 95% protective efficacy was calculated for the vaccinee 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 study¹⁹ 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.⁵ 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.⁹

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.² 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 study¹⁹ 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.⁵ 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.² 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.^{5,10-15}

Seroconversion as defined by the acquisition of any detectable varicella antibodies (based on assay cutoff that generally corresponds to 0.6 units in the gpELISA, a highly sensitive assay which is not commercially available), was observed in 98% of vaccinees at approximately 4 to 6 weeks postvaccination in 9610 susceptible children 12 months to 12 years of age 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.¹⁶ 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 the National Advisory Committee on Immunization (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.¹⁷

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 PRECAUTIONS, Transmission).^{5,18} 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 without a varicella-like rash has been reported but has not been confirmed (see PRECAUTIONS).

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.¹⁹ 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).

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 Frosst 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.

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.

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Liquid PedvaxHIB[®] is a Registered Trademark of Merck & Co., Inc. Used under license.

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

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.

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 PRECAUTIONS, Use in Pregnancy).

WARNINGS

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.

PRECAUTIONS

General

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactoid reaction occur.²¹

The duration of protection from varicella infection after vaccination with VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) is unknown.

The United States Advisory Committee on Immunization Practices (ACIP)²² recommends the vaccine for use in susceptible persons following exposure to varicella (if used within 3 days, and possibly up to 5 days of exposure).^{17,20}

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 without a varicella-like rash has been reported but has not been confirmed.

*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.^{17,20}

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

- Immunocompromised individuals
- Pregnant women without documented history of chickenpox or laboratory evidence of prior infection
- Newborn infants of mothers without documented history of chickenpox or laboratory evidence of prior infection

Use in Children

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).

Use in Pregnancy

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 Frosst Canada Ltd.

Nursing Mothers

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

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, 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 or Tetramune. If varicella vaccine (Oka/Merck) is not given concomitantly with M-M-R® II, one month interval between the two live virus vaccines should be observed.²³

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® using separate sites and syringes and with OPV (oral poliovirus vaccine).

ADVERSE REACTIONS

Clinical Studies

In clinical trials, varicella vaccine (Oka/Merck) was administered to approximately 17,000 healthy children, adolescents, and adults. Varicella vaccine (Oka/Merck) was generally well tolerated.^{10,17,24}

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.⁵

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.²⁵

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

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

Body as a Whole

Anaphylaxis in individuals with or without allergic history.

Hemic and Lymphatic System

Thrombocytopenia (including ITP); lymphadenopathy.

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.

DOSAGE AND 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.²⁶ Persistence of antibody and efficacy in those receiving intramuscular injections have not been defined.

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 elected date and a second 0.5 mL dose 4 to 8 weeks later.

Storage and Reconstitution

VARIVAX[®] III has a shelf-life of 24 months and should be stored at a temperature of 2°C to 8°C or colder prior to use. Vaccine may be stored at room temperature (23°C to 27°C) for a maximum of 6 hours prior to reconstitution. The vaccine may also be stored in a freezer; if subsequently transferred to a refrigerator, **THE VACCINE SHOULD NOT BE REFROZEN (see PHARMACEUTICAL INFORMATION, Stability and Storage Recommendations).** **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).

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.

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

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, colorless 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 FREEZE RECONSTITUTED VACCINE.**

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

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.

PHARMACEUTICAL INFORMATION

COMPOSITION

Active Ingredients

VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]), when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.5 mL dose contains a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus when reconstituted and stored at room temperature for 90 minutes.

Non-Medicinal Ingredients

Each 0.5 mL dose contains: approximately 18 mg of sucrose, 8.9 mg of hydrolyzed gelatin, 3.6 mg of urea, 2.3 mg of sodium chloride, 0.36 mg of monosodium L-glutamate, 0.33 mg of sodium phosphate dibasic, 57 µg of potassium phosphate monobasic, 57 µg of potassium chloride. 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. The product contains no preservative.

Stability and Storage Recommendations

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.

Before reconstitution, VARIVAX® III has a shelf life of 24 months and should be stored at a temperature of 2°C to 8°C or colder. Vaccine may be stored at room temperature (23°C to 27°C) for a maximum of 6 hours prior to reconstitution. The vaccine may also be stored in a freezer; if subsequently transferred to a refrigerator, **THE VACCINE SHOULD NOT BE REFROZEN. 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.

VARIVAX® III has a minimum potency level of approximately 1350 PFU 90 minutes after reconstitution at room temperature (20°C to 25°C).

AVAILABILITY OF DOSAGE FORMS

VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) is supplied as follows: (1) single-dose vial (0.5 mL) of lyophilized vaccine, (2) a vial (0.7 mL) of diluent, (3) a box of 10 single-dose vials (0.5 mL) of lyophilized vaccine, and (4) a box of 10 vials (0.7 mL) of diluent.

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