

VARIVAX®

Varicella Virus Vaccine Live Refrigerator-stable formulation

DESCRIPTION

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

Refrigerator-stable VARIVAX, when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.5 mL dose contains the following: a minimum of 1350 plaque forming units (PFU) of Oka/Merck varicella virus when reconstituted and stored at room temperature for 30 minutes, approximately 18 mg of sucrose, 8.9 mg 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 mcg of potassium phosphate monobasic, 57 mcg of potassium chloride. The product also contains residual components of MRC-5 cells including DNA and protein and trace quantities of neomycin and bovine calf serum from MRC-5 culture media. The product contains no preservative.

Vaccine Vial

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 2 to 8°C or colder (36 to 46°F or colder).

Before reconstitution, refrigerator-stable VARIVAX has a shelf-life of 18 months when refrigerated at 2 to 8°C or colder (36 to 46°F or colder). The vaccine may also be stored in a freezer; if subsequently transferred to a refrigerator, **THE VACCINE SHOULD NOT BE REFROZEN** (see **HOW SUPPLIED, Stability and Storage**).

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

Diluent Vial

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

CLINICAL PHARMACOLOGY

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 $\geq 100^{\circ}\text{F}$) in up to 70% of individuals.^{1,2} Approximately 3.5 million cases of varicella occurred annually from 1980 to 1994 in the United States with the peak incidence occurring in children five to nine years of age.³ The incidence rate of chickenpox in the total population was 8.3 to 9.1% per year in children 1 to 9 years of age before licensure of the frozen formulation of VARIVAX [hereafter called VARIVAX].^{4,6} The attack rate of wild-type varicella following household exposure among healthy susceptible children was shown to be 87% in unvaccinated populations.² 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.

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 trials⁵ of VARIVAX at doses ranging from 1000 to 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 VARIVAX was evaluated in three different ways: 1) by comparing chickenpox rates in vaccinees versus historical controls, 2) by assessment of protection from disease following household exposure, and 3) by a placebo-controlled, double-blind clinical trial.

In early clinical trials,⁵ a total of 4240 children 1 to 12 years of age received 1000 to 1625 PFU of attenuated virus per dose of VARIVAX 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 was acquired by passive follow-up. It was observed that 0.3 to 3.8% of vaccinees per year reported chickenpox (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.¹⁹ 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.⁷

Among a subset of vaccinees who were actively followed in these early trials for up to nine 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 a mild form of chickenpox (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 chickenpox in unvaccinated individuals in the calculation of efficacy.

In later clinical trials⁵, a total of 1114 children 1 to 12 years of age received 2900-9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to 10 years post single-dose vaccination. It was observed that 0.2%-2.3% of vaccinees per year reported breakthrough chickenpox 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.^{4,6,19} 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 10 years postvaccination, 95 individuals were exposed to an unvaccinated individual with wild-type chickenpox in a household setting. There were no reports of breakthrough chickenpox in 92% (87/95) of exposed children, while 8% (8/95) reported a mild form of chickenpox (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 chickenpox in unvaccinated individuals in the calculation of efficacy.

Although no placebo-controlled trial was carried out with refrigerator-stable VARIVAX, a placebo-controlled trial was conducted using a prior formulation containing 17,000 PFU per dose.^{4,8} In this trial, a single dose of VARIVAX protected 96 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=163 vaccine, n=161 placebo), 96% protective efficacy was calculated for the vaccine group as compared to placebo.

There are insufficient data to assess the rate of protection against the complications of chickenpox (e.g., encephalitis, hepatitis, pneumonia) in children.

Two-Dose Regimen in Children

In a clinical trial, a total of 2216 children 12 months to 12 years of age with a negative history of varicella were randomized to receive either 1 dose of VARIVAX (n=1114) or 2 doses of VARIVAX (n=1102) given 3 months apart. Subjects were actively followed for varicella, any varicella-like illness, or herpes zoster and any exposures to varicella or herpes zoster on an annual basis for 10 years after vaccination. Persistence of VZV antibody was measured annually for 9 years. Most cases of varicella reported in recipients of 1 dose or 2 doses of vaccine were mild.²⁶ The estimated vaccine efficacy for the 10-year observation period was 94% for 1 dose and 98% for 2 doses ($p < 0.001$). This translates to a 3.4-fold lower risk of developing varicella >42 days postvaccination during the 10-year observation period in children who received 2 doses than in those who received 1 dose (2.2% vs. 7.5%, respectively).

Clinical Data in Adolescents and Adults

Two-Dose Regimen in Adolescents and Adults

In early clinical trials, a total of 796 adolescents and adults received 905 to 1230 PFU of attenuated virus per dose of VARIVAX and have been followed for up to six years following 2-dose vaccination. A total of 50 clinical varicella cases were reported >42 days following 2-dose vaccination. Based on passive follow-up, the annual chickenpox breakthrough event rate ranged from <0.1 to 1.9%. The median of the maximum total number of lesions ranged from 15 to 42 per year.

Although no placebo-controlled trial was carried out in adolescents and adults, the protective efficacy of VARIVAX was determined by evaluation of protection when vaccinees received 2 doses of VARIVAX 4 or 8 weeks apart and were subsequently exposed to chickenpox in a household setting.⁵ Among the subset of vaccinees who were actively followed in these early trials for up to six years, 76 individuals had household exposure to chickenpox. There were no reports of breakthrough chickenpox in 83% (63/76) of exposed vaccinees, while 17% (13/76) reported a mild form of chickenpox. Among 13 vaccinated individuals who developed breakthrough chickenpox after a household exposure, 62% (8/13) of the cases reported maximum total number of lesions <50, while no individual reported >75 lesions. The attack rate of unvaccinated adults exposed to a single contact in a household has not been previously studied. Utilizing the previously reported historical attack rate of 87% for wild-type varicella following household exposure to chickenpox among unvaccinated children in the calculation of efficacy, this represents an approximate 80% reduction in the expected number of cases in the household setting.

In later clinical trials, a total of 220 adolescents and adults received 3315 to 9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to six years following 2-dose vaccination. A total of 3 clinical varicella cases were reported >42 days following 2-dose vaccination. Two cases reported <50 lesions and none reported >75. The annual chickenpox breakthrough event rate ranged from 0 to 1.2%. Among the subset of vaccinees who were actively followed in these later trials for up to five years, 16 individuals were exposed to an unvaccinated individual with wild-type chickenpox in a household setting. There were no reports of breakthrough chickenpox among the exposed vaccinees.

There are insufficient data to assess the rate of protection of VARIVAX against the serious complications of chickenpox in adults (e.g., encephalitis, hepatitis, pneumonitis) and during pregnancy (congenital varicella syndrome).

Immunogenicity of VARIVAX

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

Clinical trials with several formulations of the vaccine containing attenuated virus ranging from 1000 to 50,000 PFU per dose have demonstrated that VARIVAX induces detectable immune responses in a high proportion of individuals and is generally well tolerated in healthy individuals ranging from 12 months to 55 years of age.^{4,5,9-15}

Seroconversion is defined by the acquisition of any detectable VZV antibodies, based on an optical density (OD) cutoff, corresponding approximately to a lower limit of 0.6 glycoprotein enzyme-linked immunosorbent assay (gpELISA) units/mL.

The gpELISA is a highly sensitive assay that is not commercially available. Seroconversion was observed in 97% of vaccinees at approximately 4 to 6 weeks postvaccination in 6889 susceptible children 12 months to 12 years of age. Rates of breakthrough disease were significantly lower among children with VZV antibody titers ≥ 5 gpELISA units/mL compared with children with titers < 5 gpELISA units/mL. Titers ≥ 5 gpELISA units/mL were induced in approximately 76% of children vaccinated with a single dose of vaccine at 1000 to 17,000 PFU per dose.

Immunogenicity of refrigerator-stable VARIVAX (6550 PFU per dose, n=320 and 28,400 PFU per dose, n=315) was compared with that of the previously licensed formulation (9189 PFU per dose, n=323) in a double-blind, randomized, multicenter study in U.S. 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 titers < 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 titers ≥ 5 gpELISA units in 93.3%, 93.8%, and 95.1% of subjects, respectively.

VARIVAX also induces cell-mediated immune responses in vaccinees. The relative contributions of humoral immunity and cell-mediated immunity to protection from chickenpox are unknown.

Two-Dose Regimen in Children

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

	VARIVAX 1-Dose Regimen (N = 1114)	VARIVAX 2-Dose Regimen (N = 1102)	
	6 Weeks Postvaccination	6 Weeks Postdose 1	6 Weeks Postdose 2
Seroconversion Rate	98.9% (882/892)	99.5% (847/851)	99.9% (768/769)
Percent with VZV Antibody Titer ≥ 5 gpELISA units/mL	84.9% (757/892)	87.3% (743/851)	99.5% (765/769)
Geometric mean titers (gpELISA units/mL)	12.0	12.8	141.5

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

Two-Dose Regimen in Adolescents and Adults

In a multicenter study involving susceptible adolescents and adults 13 years of age and older, 2 doses of VARIVAX administered 4 to 8 weeks apart induced a seroconversion rate of approximately 75% in 539 individuals 4 weeks after the first dose and of 99% in 479 individuals 4 weeks after the second dose. The average antibody response in vaccinees who received the second dose 8 weeks after the first dose was higher than that in vaccinees who received the second dose 4 weeks after the first dose. In another multicenter study involving adolescents and adults, 2 doses of VARIVAX administered 8 weeks apart induced a seroconversion rate of 94% in 142 individuals 6 weeks after the first dose and 99% in 122 individuals 6 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 clinical studies involving healthy children who received 1 dose of vaccine, detectable VZV antibodies were present in 99.0% (3886/3926) at 1 year, 99.3% (1555/1566) at 2 years, 98.6% (1106/1122) at 3 years, and 99.4% (1168/1175) at 4 years, 99.2% (737/743) at 5 years, 100% (142/142) at 6 years, 97.4% (38/39) at 7 years, 100% (34/34) at 8 years, and 100% (16/16) at 10 years postvaccination.

Two-Dose Regimen in Children

In recipients of 1 dose of VARIVAX over 9 years of follow-up, the geometric mean titer (GMT) and the percent of subjects with VZV antibody titers ≥ 5 gpELISA units/mL generally increased. The GMTs and percent of subjects with VZV antibody titers ≥ 5 gpELISA units/mL in the 2-dose recipients were higher than those in the 1-dose recipients for the first year of follow-up and generally comparable thereafter. The cumulative rate of VZV antibody persistence with both regimens remained very high at Year 9 (99.0% for the 1-dose group and 98.8% for the 2-dose group).

Two-Dose Regimen in Adolescents and Adults

In clinical studies involving healthy adolescents and adults who received 2 doses of vaccine, detectable VZV antibodies 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, 97.4% (76/78) at 5 years, and 100% (34/34) 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 VARIVAX in the absence of wild-type boosting is unknown. VARIVAX also induces cell-mediated immune responses in vaccinees. The relative contributions of humoral immunity and cell-mediated immunity to protection from chickenpox are 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*).^{4,16} Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from vaccinees who do not develop a varicella-like rash has also been reported.

Herpes Zoster

Overall, 9454 healthy children (12 months to 12 years of age) and 1648 adolescents and adults (13 years of age and older) have been vaccinated with VARIVAX in clinical trials. Eight cases of herpes zoster have been reported in children during 42,556 person years of follow-up in clinical trials, resulting in a calculated incidence of at least 18.8 cases per 100,000 person years. The completeness of this reporting has not been determined. One case of herpes zoster has been reported in the adolescent and adult age group during 5410 person years of follow-up in clinical trials resulting in a calculated incidence of 18.5 cases per 100,000 person years.⁵

All 9 cases were mild and without sequelae. Two cultures (one child and one adult) obtained from vesicles were positive for wild-type VZV as confirmed by restriction endonuclease analysis.^{5,17} The long-term effect of VARIVAX 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 herpes 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.^{5,18,19} The incidence of herpes zoster in adults who have had wild-type varicella infection is higher than that in children.²⁰

Reye's Syndrome

Reye's syndrome has occurred in children and adolescents following wild-type varicella infection, the majority of whom had received salicylates.²¹ 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.

Studies with Other Vaccines

In combined clinical studies involving 1080 children 12 to 36 months of age, 653 received VARIVAX and M-M-R II 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 VARIVAX concomitantly with M-M-R II at separate sites and those who received VARIVAX and M-M-R II at different times (see PRECAUTIONS, *Drug Interactions*, *Use with Other Vaccines*).⁵

In a clinical study involving 318 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 144 received M-M-R II concomitantly with booster doses of DTaP and OPV followed by VARIVAX 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and VZV and the percentage of vaccinees whose titers were boosted for diphtheria, tetanus, pertussis, and polio were comparable between the two groups, but anti-VZV 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.⁵

In another clinical study involving 307 children 12 to 18 months of age, 150 received an investigational vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with a booster dose of PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] while 130 received M-M-R II concomitantly with a booster dose of PedvaxHIB followed by VARIVAX 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and VZV, and geometric mean titers for PedvaxHIB were comparable between the two groups, but anti-VZV levels were decreased when the investigational vaccine containing varicella was administered concomitantly with PedvaxHIB. No clinically significant differences in adverse reactions were seen between the two groups.⁵

In a clinical study involving 609 children 12 to 23 months of age, 305 received VARIVAX, 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 concomitantly at separate sites, followed by VARIVAX 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella and VZV were similar between the two groups. Postvaccination GMTs for all antigens were similar in both treatment groups except for VZV, which was lower when VARIVAX was administered concomitantly with M-M-R II and TETRAMUNE, but within the range of GMTs seen in previous clinical experience when VARIVAX was administered alone. At 1 year postvaccination, GMTs for measles, mumps, rubella, VZV 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 COMVAX® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) vaccine], M-M-R II, and VARIVAX concomitantly at separate sites, and 412 received COMVAX followed by M-M-R II and VARIVAX given concomitantly at separate sites, 6 weeks later. At six weeks postvaccination, the immune responses for the subjects who received the concomitant doses of COMVAX, M-M-R II, and VARIVAX were similar to those of the subjects who received COMVAX followed

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6 weeks later by M-M-R II and VARIVAX with respect to all antigens administered. All three 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 three vaccines were administered concomitantly versus 6 weeks apart.

Refrigerator-stable VARIVAX is recommended for subcutaneous administration. However, during clinical trials, some children received VARIVAX intramuscularly resulting in seroconversion rates similar to those in children who received the vaccine by the subcutaneous route.²² Persistence of antibody and efficacy in those receiving intramuscular doses have not been defined.

INDICATIONS AND USAGE

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

The duration of protection of refrigerator-stable VARIVAX is unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination.²⁶ In addition, a boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella as well as following a second dose of varicella vaccine (Oka/Merck).⁵

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

Vaccination with refrigerator-stable VARIVAX may not result in protection of all healthy, susceptible children, adolescents, and adults (see CLINICAL PHARMACOLOGY).

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 virus²³; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

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

Active untreated tuberculosis.

Any febrile respiratory illness or other active febrile infection.

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

PRECAUTIONS

General

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

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

It is not known whether refrigerator-stable VARIVAX given immediately after exposure to wild-type varicella virus will prevent illness.

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).²⁴

Following administration of refrigerator-stable VARIVAX, any immune globulin, including VZIG, should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination.²⁴

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with refrigerator-stable VARIVAX as Reye's syndrome has been reported following the use of salicylates during wild-type varicella infection (see CLINICAL PHARMACOLOGY, *Reye's Syndrome*).

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

Care is to be taken by the health care provider for safe and effective use of refrigerator-stable VARIVAX.

The health care provider should question the patient, parent, or guardian about reactions to a previous dose of refrigerator-stable VARIVAX or a similar product.

The health care provider should obtain the previous immunization history of the vaccinee.

Refrigerator-stable VARIVAX should not be injected into a blood vessel.

Vaccination should be deferred in patients with a family history of congenital or hereditary immunodeficiency until the patient's own immune system has been evaluated.

A separate sterile needle and syringe should be used for administration of each dose of refrigerator-stable VARIVAX to prevent transfer of infectious diseases.

Needles should be disposed of properly and should not be recapped.

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 a mother who did not develop a varicella-like rash to her newborn infant 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 and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

Information for Patients

The health care provider should inform the patient, parent, or guardian of the benefits and risks of refrigerator-stable VARIVAX.

Patients, parents, or guardians should be instructed to report any adverse reactions to their health care provider.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.²⁵ The VAERS toll-free number for VAERS forms and information is 1-800-822-7967.

Pregnancy should be avoided for three months following vaccination.

Drug Interactions

See PRECAUTIONS, *General*, regarding the administration of immune globulins, salicylates, and transfusions.

Drug Interactions, Use with Other Vaccines

Results from clinical studies indicate that refrigerator-stable VARIVAX can be administered concomitantly with M-M-R II, COMVAX, or TETRAMUNE (see CLINICAL PHARMACOLOGY, *Studies with Other Vaccines*).

Limited data from an experimental product containing varicella vaccine suggest that refrigerator-stable VARIVAX can be administered concomitantly with DTaP and PedvaxHIB using separate sites and syringes (see CLINICAL PHARMACOLOGY, *Studies with Other Vaccines*).⁵ However, there are no data relating to simultaneous administration of refrigerator-stable VARIVAX with DTP or OPV.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with refrigerator-stable VARIVAX. It is also not known whether refrigerator-stable VARIVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, refrigerator-stable VARIVAX should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see CONTRAINDICATIONS).

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to VARIVAX. Patients and health care providers are encouraged to report any exposure to VARIVAX during pregnancy by calling 1-800-986-8999.

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 refrigerator-stable VARIVAX is administered to a nursing woman. (See PRECAUTIONS, *Transmission*.)

Geriatric Use

Clinical studies of VARIVAX did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

Pediatric Use

No clinical data are available on safety or efficacy of refrigerator-stable VARIVAX in children less than one year of age, and administration to infants under twelve months of age is not recommended.

ADVERSE REACTIONS

In clinical trials,^{4,5,9-15} VARIVAX was administered to over 11,000 healthy children, adolescents, and adults. VARIVAX was generally well tolerated.

In a double-blind, placebo-controlled study among 914 healthy children and adolescents who were serologically confirmed to be susceptible to varicella, the only adverse reactions that occurred at a significantly ($p < 0.05$) greater rate in vaccine recipients than in placebo recipients were pain and redness at the injection site.⁴

Children 1 to 12 Years of Age

One-Dose Regimen in Children

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

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

Reaction	N	Post Dose 1	Peak Occurrence in Postvaccination Days
Fever $\geq 102^{\circ}\text{F}$ (38.9°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, arthralgia, eczema/dry skin/dermatitis, constipation, itching.

Pneumonitis has been reported rarely ($< 1\%$) in children vaccinated with VARIVAX; a causal relationship has not been established.

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

Clinical safety of refrigerator-stable VARIVAX ($n=635$) was compared with that of the previously licensed formulation of VARIVAX ($n=323$) for 42 days postvaccination in U.S. children 12 to 23 months of age. The safety profiles were comparable for the two different formulations. Pain/tenderness/soreness (24.8 to 28.9%) and erythema (18.4 to 21.0%) were the most commonly reported local reactions. The most common systemic adverse events (reported by $\geq 10\%$ of subjects in one or more treatment groups, irrespective of causal relationship to vaccination) were: fever $\geq 102^{\circ}\text{F}$, 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

Nine hundred eighty one (981) subjects in a clinical trial received 2 doses of VARIVAX 3 months apart and were actively followed for 42 days after each dose. The 2-dose regimen of varicella vaccine was generally well tolerated, with a safety profile generally comparable to that of the 1-dose regimen. The incidence of injection-site clinical complaints (primarily erythema and swelling) observed in the first 4 days following vaccination was slightly higher Postdose 2 (overall incidence 25.4%) than Postdose 1 (overall incidence 21.7%), whereas the incidence of systemic clinical complaints in the 42-day follow-up period was lower Postdose 2 (66.3%) than Postdose 1 (85.8%).

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

Reaction	N	Post Dose 1	Peak Occurrence in Postvaccination Days	N	Post Dose 2	Peak Occurrence in Postvaccination Days
Fever ≥100°F (37.8°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%	0-6
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 (≥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, diarrhea, stiff neck, irritability/nervousness, 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.

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

The following additional adverse reactions 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 edema, facial edema, and peripheral edema.

Hemic and Lymphatic System

Aplastic anemia, thrombocytopenia (including idiopathic thrombocytopenic purpura (ITP)).

Infections and Infestations

Varicella (vaccine strain).

Nervous/Psychiatric

Encephalitis; cerebrovascular accident; transverse myelitis; Guillain-Barré syndrome; Bell's palsy; ataxia; non-febrile seizures; aseptic meningitis; dizziness; paresthesia.

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

Do not inject intravascularly

Children

Children 12 months to 12 years of age should receive a 0.5-mL dose administered subcutaneously. If a second 0.5-mL dose is administered, it should be given a minimum of 3 months later.

Adolescents and 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.

Refrigerator-stable VARIVAX is for subcutaneous administration. The outer aspect of the upper arm (deltoid region) is the preferred site of injection.

To reconstitute the vaccine, first withdraw 0.7 mL of diluent into a syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into the syringe and inject the total volume (about 0.5 mL) of reconstituted vaccine subcutaneously, preferably into the outer aspect of the upper arm (deltoid region) or the anterolateral thigh. **IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.**

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

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

To reconstitute the vaccine, use only the Merck sterile diluent supplied with refrigerator-stable VARIVAX, since it is free of preservatives or other anti-viral substances which might inactivate the vaccine virus.

Do not freeze reconstituted vaccine.

Do not give immune globulin, including Varicella Zoster Immune Globulin, concurrently with refrigerator-stable VARIVAX (see also PRECAUTIONS).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Refrigerator-stable VARIVAX when reconstituted is a clear, colorless to pale yellow liquid.

HOW SUPPLIED

No. 4979/4309 — Refrigerator-stable VARIVAX is supplied as follows: (1) a single-dose vial of lyophilized vaccine (package A), **NDC 0006-4979-00**; and (2) a box of 10 vials of diluent (package B).

No. 4055/4309 — Refrigerator-stable VARIVAX is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC 0006-4055-00**; and (2) a box of 10 vials of diluent (package B).

Stability

Refrigerator-stable VARIVAX has a minimum potency level of approximately 1350 PFU 30 minutes after reconstitution at room temperature (20 to 25°C, 68 to 77°F).

For information regarding stability under conditions other than those recommended, call 1-800-9-VARIVAX.

Storage

Vaccine Vial

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 2 to 8°C or colder (36 to 46°F or colder). Before reconstitution, refrigerator-stable VARIVAX has a shelf-life of 18 months when refrigerated at 2 to 8°C or colder (36 to 46°F or colder). The vaccine may also be stored in a freezer; if subsequently transferred to a refrigerator, **THE VACCINE SHOULD NOT BE REFROZEN.**

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

Diluent Vial

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

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