

طبقاً لقرار اللجنة العلمية المتخصصة للمستحضرات الحيوية
بجلستها من يوم الأحد ١٧/١٢/٢٠١٧

VARIVAX®
Varicella Virus Vaccine Live
Suspension for Intramuscular or subcutaneous injection

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VARIVAX is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older.

2 DOSAGE AND ADMINISTRATION

Intramuscular or subcutaneous administration only

2.1 Dose and Schedule

A single dose of VARIVAX is approximately 0.5 mL.

Children (12 months to 12 years of age)

The first dose is administered at 12 to 15 months of age but may be given anytime through 12 years of age.

The second dose is administered at 4 to 6 years of age. At least 3 months should elapse between a dose of varicella-containing vaccine and VARIVAX.

At least 1 month should elapse between a dose of measles-containing vaccine and a dose of VARIVAX if the vaccines are not given concurrently [see *Clinical Studies (14.1)*].

Adolescents (≥13 years of age) and Adults

Two doses of VARIVAX are administered at a minimum interval of 4 weeks [see *Clinical Studies (14.1)*].

2.2 Reconstitution Instructions

Use a sterile syringe free of preservatives, antiseptics, and detergents for each reconstitution and injection of VARIVAX because these substances may inactivate the vaccine virus. When reconstituting the vaccine, use only the sterile diluent supplied with VARIVAX. The sterile diluent does not contain preservatives or other anti-viral substances which might inactivate the vaccine virus.

To reconstitute the vaccine, withdraw the total volume of supplied sterile diluent and inject into the lyophilized vaccine vial. Agitate to dissolve completely. Discard if the lyophilized vaccine cannot be dissolved.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored. Visually inspect the vaccine before and after reconstitution prior to administration. Before reconstitution, the lyophilized vaccine is a white compact crystalline plug. VARIVAX, when reconstituted, is a clear, colorless to pale yellow liquid.

Withdraw the entire amount of reconstituted vaccine, inject the total volume and discard vial.

To minimize loss of potency, administer VARIVAX immediately after reconstitution. Discard if reconstituted vaccine is not used within 30 minutes.

Do not freeze reconstituted vaccine.

Do not combine VARIVAX with any other vaccine through reconstitution or mixing.

2.3 Administration

Inject the vaccine intramuscularly or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

VARIVAX is a suspension for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent [see *Dosage and Administration (2.2)* and *How Supplied/Storage and Handling (16)*]. A single dose after reconstitution is approximately 0.5 mL.

4 CONTRAINDICATIONS

4.1 Severe Allergic Reaction

Do not administer VARIVAX to individuals with a history of anaphylactic or severe allergic reaction to any component of the vaccine (including neomycin and gelatin) or to a previous dose of a varicella-containing vaccine.

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نشرة معتمدة: ٢٠١٧/١٢/٢٠١٧
تاريخ: ٢٠١٧/١٢/٢٠١٧

4.2 Immunosuppression

Do not administer VARIVAX to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy.

Disseminated varicella disease and extensive vaccine-associated rash have been reported in individuals who are immunosuppressed or immunodeficient who were inadvertently vaccinated with a varicella-containing vaccine.

4.3 Moderate or Severe Febrile Illness

Do not administer VARIVAX to individuals with an active febrile illness with fever $>101.3^{\circ}\text{F}$ ($>38.5^{\circ}\text{C}$).

4.4 Active Untreated Tuberculosis

Do not administer VARIVAX to individuals with active, untreated tuberculosis (TB).

4.5 Pregnancy

Do not administer VARIVAX to individuals who are pregnant or planning on becoming pregnant in the next 3 months. Wild-type varicella is known to cause fetal harm [see *Use in Specific Populations* (8.1) and *Patient Counseling Information* (17)].

5 WARNINGS AND PRECAUTIONS

5.1 Family History of Immunodeficiency

Vaccination should be deferred in individuals with a family history of congenital or hereditary immunodeficiency until the individual's immune status has been evaluated and the individual has been found to be immunocompetent.

5.2 Use in HIV-Infected Individuals

The Advisory Committee on Immunization Practices (ACIP) has recommendations on the use of varicella vaccine in HIV-infected individuals.

5.3 Risk of Vaccine Virus Transmission

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

Due to the concern for transmission of vaccine virus, vaccine recipients should attempt to avoid whenever possible close association with susceptible high-risk individuals for up to six weeks following vaccination with VARIVAX. Susceptible high-risk individuals include:

- Immunocompromised individuals;
- Pregnant women without documented history of varicella or laboratory evidence of prior infection;
- Newborn infants of mothers without documented history of varicella or laboratory evidence of prior infection and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

5.4 Immune Globulins and Transfusions

Immune Globulins (IG) and other blood products should not be given concomitantly with VARIVAX [see *Drug Interactions* (7.2)]. These products may contain antibodies that interfere with vaccine virus replication and decrease the expected immune response.

The ACIP has specific recommendations for intervals between administration of antibody-containing products and live virus vaccines.

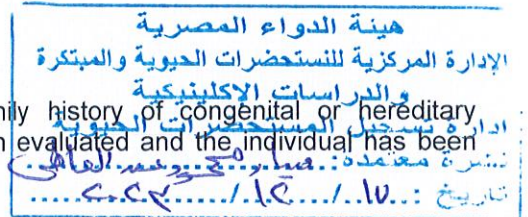
5.5 Salicylate Therapy

Avoid use of salicylates (aspirin) or salicylate-containing products in children and adolescents 12 months through 17 years of age for six weeks following vaccination with VARIVAX because of the association of Reye syndrome with salicylate therapy and wild-type varicella infection [see *Drug Interactions* (7.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.



In clinical trials, VARIVAX was administered subcutaneously to over 11,000 healthy children, adolescents, and adults.

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.

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 shown in Table 1:

Table 1: Fever, Local Reactions, and Rashes (%) in Children 1 to 12 Years of Age 0 to 42 Days After Receipt of a Single Dose of VARIVAX

Reaction	N	% Experiencing Reaction	Peak Occurrence During Postvaccination Days
Fever $\geq 102.0^{\circ}\text{F}$ (38.9°C) Oral	8824	14.7%	0 to 42
Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, induration, stiffness)	8913	19.3%	0 to 2
Varicella-like rash (injection site)	8913	3.4%	8 to 19
Median number of lesions		2	
Varicella-like rash (generalized)	8913	3.8%	5 to 26
Median number of lesions		5	

In addition, adverse events occurring at a rate of $\geq 1\%$ are listed in decreasing order of frequency: upper respiratory illness, cough, irritability, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, headache, malaise, abdominal pain, other rash, nausea, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions (including allergic rash, hives), stiff neck, arthralgia, itching.

Pneumonitis has been reported rarely ($< 1\%$) in children vaccinated with VARIVAX.

Febrile seizures have occurred at a rate of $< 0.1\%$ in children vaccinated with VARIVAX.

Clinical safety of refrigerator-stable VARIVAX ($n=635$) was compared with that of the licensed frozen 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 $\geq 102.0^{\circ}\text{F}$, 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 events.

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 had a safety profile comparable to that of the 1-dose regimen. The overall incidence of injection-site clinical complaints (primarily erythema and swelling) observed in the first 4 days following vaccination was 25.4% Postdose 2 and 21.7% Postdose 1, whereas the overall incidence of systemic clinical complaints in the 42-day follow-up period was lower Postdose 2 (66.3%) than Postdose 1 (85.8%).

Adolescents (13 Years of Age and Older) and Adults

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 frequencies of fever, injection-site complaints, or rashes are shown in Table 2.

Table 2: Fever, Local Reactions, and Rashes (%) in Adolescents and Adults 0 to 42 Days After Receipt of VARIVAX

Reaction	N	% Post Dose 1	Peak Occurrence in Postvaccination Days	N	% Post Dose 2	Peak Occurrence in Postvaccination Days
Fever $\geq 100.0^{\circ}\text{F}$ (37.8°C) Oral	1584	10.2%	14 to 27	956	9.5%	0 to 42
Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness)	1606	24.4%	0 to 2	955	32.5%	0 to 2
Varicella-like rash (injection site)	1606	3.1%	6 to 20	955	1%	0 to 6
Median number of lesions		2			2	
Varicella-like rash (generalized)	1606	5.5%	7 to 21	955	0.9%	0 to 23
Median number of lesions		5			5.5	

In addition, adverse events reported at a rate of $\geq 1\%$ are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, diarrhea, stiff neck, irritability, lymphadenopathy, chills, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, lower respiratory illness, allergic reactions (including allergic rash, hives).

In a randomized open-label clinical trial (NCT00432523), conducted in France and Germany, 752 children 12 months through 18 months of age received M-M-R II concomitantly administered with VARIVAX at a separate site, by either the intramuscular ($n=374$) or subcutaneous ($n=378$) route. In the overall population, 55.3% were male and the median age was 13.2 months. Local and systemic solicited adverse reactions were recorded by parents or guardians using standardized diary cards. Local solicited reactions were recorded for 4 days after vaccination, and systemic solicited adverse reactions were recorded for 42 days after vaccination. In the event that a participant experienced a rash or a mumps-like illness, parents and/or guardians were instructed to contact the investigator for an examination as soon as possible and no later than 72 hours following onset of symptoms. The nature of any rash was characterized by principal investigator either as a measles-like, rubella-like, varicella-like or "other". Study investigators reviewed the diary card with the participant or participant's legal guardian 42 days vaccination to ensure consistency with protocol definitions. Table 3 below presents the frequency of solicited adverse reactions based on the final assessment by the study investigators.

Table 3: Proportion of Participants Reporting at Solicited Adverse Reactions Following Vaccination with VARIVAX Concomitantly Administered with M-M-R II, by the Intramuscular or Subcutaneous Route

	Intramuscular N=374 %	Subcutaneous N=376 %
Solicited local reactions at Varivax injection site (Days 0 to 4)*		
Erythema [†]	8.8	16.8
Mild	8.0	12.8
Moderate	0.5	3.7
Severe	0	0
Missing	0.3	0.3
Pain [†]	7.0	8.5
Mild	4.8	7.2
Moderate	2.1	1.3
Severe	0	0
Swelling [†]	3.2	4.8
Mild	1.6	3.5
Moderate	1.1	0.5
Severe	0	0
Missing	0.5	0.8
Solicited systemic reactions (Days 0 to 42)		
Measles-like rash (Days 0 to 42) [§]	2.9	2.7
Rubella-like rash (Days 0 to 42) [§]	2.7	2.7
Varicella-like rash (Days 0 to 42) [§]	0.5	3.2
Mumps-like illness (Days 0 to 42)	0	0.3
Fever (temperature $\geq 38.0^{\circ}\text{C}$) (Days 0 to 42) ^{¶, #}	66.5	66.8
38.0-38.5°C	20.4	22.2

>38.5-39.0°C	17.4	16.6
>39.0-39.5°C	14.2	13.4
>39.5-40.0°C	11.8	11.0
>40.0°C	2.7	3.7

N=total number of participants in the group

* During the post vaccination monitoring period (0-42 days), eight participants experienced a varicella-like injection-site rash at the VARIVAX injection site. All were reported in the subcutaneous group.

† Intensity of injection site reaction: mild or ≤ 2.5 cm; moderate or > 2.5 to ≤ 5.0 cm; severe or > 5.0 cm.

‡ Intensity of pain: mild: awareness of symptom but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.

§ Testing to distinguish between rash caused by wild-type or vaccine virus was not performed. Reports of measles-, rubella-, and varicella-like rash included 3 reports of measles, 1 report of rubella, and 1 report of varicella, all with onset within 15 days post-vaccination.

¶ The percentage of fever is defined within the population who had valid temperature measurements. One participant in IM group and two participants in SC group did not have temperature measurements and were excluded from the denominator; resulting in N=373 and N=374, respectively.

In the IM Group 92.3% of fevers were documented using the rectal route of measurement and 7.7% of fevers were documented only by the axillary route of measurement. In the SC Group 89.6% of fevers were documented using the rectal route of measurement and 10.4% of fevers were documented only by the axillary route of measurement.

Unsolicited adverse events that occurred within 42 days following vaccination were recorded using diary cards supplemented by medical review. Data on unsolicited adverse events were transcribed into the study database during an on-site visit at day 42. The rates and types of reported adverse events (AEs) across groups were similar and included common clinical events that are often reported in the evaluated populations. Serious adverse events occurred at rates of 0.3% and 1% in the intramuscular and subcutaneous groups, respectively. One moderate intensity case of otitis media occurred in a participant in the subcutaneous group was considered related to the vaccination.

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. 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. 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. The incidence of herpes zoster in adults who have had wild-type varicella infection is higher than that in children.

6.2 Post-Marketing Experience

The following adverse events have been identified during post approval use of VARIVAX. Because the events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Body as a Whole

Anaphylaxis (including anaphylactic shock) and related phenomena such as angioneurotic edema, facial edema, and peripheral edema.

Eye Disorders

Necrotizing retinitis (in immunocompromised individuals).

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; meningitis; dizziness; paresthesia; syncope.

Cases of encephalitis or meningitis caused by vaccine strain varicella virus have been reported in immunocompromised and immunocompetent individuals previously vaccinated with VARIVAX months to

years after vaccination. Reported cases were commonly associated with preceding or concurrent herpes zoster rash.

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; wild-type or vaccine strain herpes zoster.

Herpes Zoster

The vaccine virus (Oka/Merck strain) contained in VARIVAX may establish latency of varicella zoster virus in immunocompetent individuals, with the potential for later development of herpes zoster.

7 DRUG INTERACTIONS

7.1 Salicylates

No cases of Reye syndrome have been observed following vaccination with VARIVAX. Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX, as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection [see *Warnings and Precautions* (5.5)].

7.2 Immune Globulins and Transfusions

Administration of immune globulins and other blood products concurrently with VARIVAX may interfere with the expected immune response [see *Warnings and Precautions* (5.4)]. The ACIP has specific recommendations for intervals between administration of antibody-containing products and live virus vaccines.

7.3 Tuberculin Skin Testing

Tuberculin skin testing, with tuberculin purified protein derivative (PPD), may be performed before VARIVAX is administered or on the same day, or at least 4 weeks following vaccination with VARIVAX, as other live virus vaccines may cause a temporary depression of tuberculin skin test sensitivity leading to false negative results.

7.4 Use with Other Vaccines

VARIVAX can be administered concurrently with other live viral vaccines. If not given concurrently, at least 1 month should elapse between a dose of a live attenuated measles virus-containing vaccine and a dose of VARIVAX. In children through the age of 12 years at least 3 months should elapse between administration of 2 doses of a live attenuated varicella virus-containing vaccine. For adolescents and adults, 2 doses of VARIVAX may be separated by 1 month [see *Dosage and Administration* (2.1)].

VARIVAX may be administered concomitantly with M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live), *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate), and hepatitis B (recombinant). Additionally, VARIVAX may be administered concomitantly with inactivated diphtheria-tetanus and acellular pertussis vaccines [see *Clinical Studies* (14.4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

VARIVAX is contraindicated for use in pregnant women because the vaccine contains live, attenuated varicella virus, and it is known that wild-type varicella virus, if acquired during pregnancy, can cause congenital varicella syndrome [see *Contraindications* (4.5) and *Patient Counseling Information* (17)]. No increased risk for miscarriage, major birth defect or congenital varicella syndrome was observed in a pregnancy exposure registry that monitored outcomes after inadvertent use. There are no relevant animal data.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively.

Human Data

A pregnancy exposure registry was maintained from 1995 to 2013 to monitor pregnancy and fetal outcomes following inadvertent administration of VARIVAX. The registry prospectively enrolled 1522 women who received a dose of VARIVAX during pregnancy or within three months prior to conception. After excluding elective terminations (n=60), ectopic pregnancies (n=1) and those lost to follow-up (n=556),

there were 905 pregnancies with known outcomes. Of these 905 pregnancies, 271 (30%) were in women who were vaccinated within the three months prior to conception. Miscarriage was reported for 10% of pregnancies (95/905), and major birth defects were reported for 2.6% of live born infants (21/819). These rates of assessed outcomes were consistent with estimated background rates. None of the women who received VARIVAX vaccine delivered infants with abnormalities consistent with congenital varicella syndrome.

8.2 Lactation

Risk Summary

It is not known whether varicella vaccine virus is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VARIVAX, and any potential adverse effects on the breastfed child from VARIVAX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

No clinical data are available on safety or efficacy of VARIVAX in children less than 12 months of age.

8.5 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.

11 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 intramuscular or subcutaneous injection. Each approximately 0.5 mL dose contains a minimum of 1350 plaque-forming units (PFU) of Oka/Merck varicella virus when reconstituted and stored at room temperature for a maximum of 30 minutes. Each approximately 0.5 mL dose also contains approximately 17 mg of sucrose, 8.3 mg hydrolyzed gelatin, 3.5 mg of urea, 2.1 mg of sodium chloride, 0.33 mg of monosodium L-glutamate, 0.30 mg of sodium phosphate dibasic, 53 mcg of potassium phosphate monobasic, and 53 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.

12 CLINICAL PHARMACOLOGY

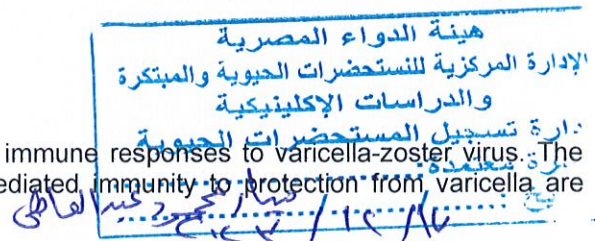
12.1 Mechanism of Action

VARIVAX induces both cell-mediated and humoral immune responses to varicella-zoster virus. The relative contributions of humoral immunity and cell-mediated immunity to protection from varicella are unknown.

12.2 Pharmacodynamics

Transmission

In the placebo-controlled efficacy 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 varicella and seroconverted, nine reported a varicella-like rash and did not seroconvert, and six had no rash but seroconverted. If vaccine virus transmission occurred, it did so at a very low rate and possibly without recognizable clinical disease in contacts. These cases may represent either wild-type varicella from community contacts or a low incidence of transmission of vaccine virus from vaccinated contacts. Post-marketing experience suggests that transmission of varicella vaccine virus (Oka/Merck) resulting in varicella infection including disseminated disease may occur rarely between vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella including healthy as well as high risk individuals [see Warnings and Precautions (5.3)].



12.4 Duration of Protection

The duration of protection of VARIVAX is unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination [see *Clinical Studies* (14.1)]. A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella which could account for the apparent long-term protection after vaccination in these studies.

14 CLINICAL STUDIES

14.1 Clinical Efficacy

The protective efficacy of VARIVAX administered subcutaneously was established by: (1) a placebo-controlled, double-blind clinical trial, (2) comparing varicella rates in vaccinees versus historical controls, and (3) assessing protection from disease following household exposure.

Clinical Data in Children

One-Dose Regimen in Children

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. In this trial, a single dose of VARIVAX protected 96 to 100% of children against varicella over a two-year period. The study enrolled healthy individuals 1 to 14 years of age (n=491 vaccine, n=465 placebo). In the first year, 8.5% of placebo recipients contracted varicella, while no vaccine recipient did, for a calculated protection rate of 100% during the first varicella season. In the second year, when only a subset of individuals agreed to remain in the blinded study (n=163 vaccine, n=161 placebo), 96% protective efficacy was calculated for the vaccine group as compared to placebo.

In early clinical trials, 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 varicella rates among studies and study sites, and much of the reported data were acquired by passive follow-up. It was observed that 0.3 to 3.8% of vaccinees per year reported varicella (called breakthrough cases). This represents an approximate 83% (95% confidence interval [CI], 82%, 84%) decrease from the age-adjusted expected incidence rates in susceptible subjects over this same period. In those who developed breakthrough varicella 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.

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 varicella. There were no reports of breakthrough varicella in 84% (150/179) of exposed children, while 16% (29/179) reported a mild form of varicella (38% [11/29] of the cases with a maximum total number of <50 lesions; no individuals with >300 lesions). This represents an 81% reduction in the expected number of varicella cases utilizing the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

In later clinical trials, a total of 1114 children 1 to 12 years of age received 2900 to 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% to 2.3% of vaccinees per year reported breakthrough varicella for up to 10 years post single-dose vaccination. This represents an estimated efficacy of 94% (95% CI, 93%, 96%), compared with the age-adjusted expected incidence rates in susceptible subjects over the same period. In those who developed breakthrough varicella postvaccination, the majority experienced mild disease, with the median of the maximum total number of lesions <50. The severity of reported breakthrough varicella, as measured by number of lesions and maximum temperature, appeared not to increase with time since vaccination.

Among a subset of vaccinees who were actively followed in these later trials for up to 10 years postvaccination, 95 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella in 92% (87/95) of exposed children, while 8% (8/95) reported a mild form of varicella (maximum total number of lesions <50; observed range, 10 to 34). This represents an estimated efficacy of 90% (95% CI, 82%, 96%) based on the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

Two-Dose Regimen in Children

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

Clinical Data in Adolescents and Adults

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 varicella 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 varicella in a household setting. Among the subset of vaccinees who were actively followed in these early trials for up to six years, 76 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 83% (63/76) of exposed vaccinees, while 17% (13/76) reported a mild form of varicella. Among 13 vaccinated individuals who developed breakthrough varicella 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 varicella 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 varicella 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 varicella in a household setting. There were no reports of breakthrough varicella among the exposed vaccinees.

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

14.2 Immunogenicity

In clinical trials, varicella antibodies have been evaluated following vaccination with formulations of VARIVAX containing attenuated virus ranging from 1000 to 50,000 PFU per dose in healthy individuals ranging from 12 months to 55 years of age.

One-Dose Regimen in Children

In prelicensure efficacy studies, 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. 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. 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.

Immunogenicity of refrigerator-stable VARIVAX (6550 PFU per dose, n=320 and 28,400 PFU per dose, n=315) administered subcutaneously was compared with that of the licensed frozen formulation of VARIVAX (9189 PFU per dose, n=323) administered subcutaneously 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 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.

In an open label clinical trial (NCT00432523) 752 children 12 through 18 months of age received VARIVAX either intramuscularly (n=374) or subcutaneously (n=378), concomitantly with M-M-R II. Antibody responses to varicella virus were measured by gpELISA using sera obtained 6 weeks postvaccination. Seroresponse rate was defined as the percentage of initially seronegative children who achieved antibody titers above the seroresponse threshold for the assay 6 weeks post vaccination. The seroresponse threshold was defined as 5 gpELISA units for anti-varicella virus antibodies. Ninety-five percent of enrolled children were seronegative to varicella virus at baseline. In the pre-specified primary analysis, seroresponse rates to varicella virus were noninferior in the intramuscular group compared to the subcutaneous group (the lower bound of the 95% confidence interval for the difference in seroresponse rates [intramuscular group minus subcutaneous group] was $\geq -10\%$). The proportions of children achieving antibody titers above the seroresponse thresholds for varicella virus were 88.4% (95% CI: 84.5, 91.6) of children in the intramuscular group and 85.5% (95% CI: 81.3, 89.0) of children in the subcutaneous.

Two-Dose Regimen in Children

In a multicenter study, 2216 healthy children 12 months to 12 years of age received either 1 dose or 2 doses of VARIVAX administered subcutaneously 3 months apart. The immunogenicity results are shown in Table 4.

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

	VARIVAX 1-Dose Regimen (N=1114)	VARIVAX 2-Dose Regimen (3 months apart) (N=1102)	
	6 Weeks Postvaccination (n=892)	6 Weeks Postdose 1 (n=851)	6 Weeks Postdose 2 (n=769)
Seroconversion Rate	98.9%	99.5%	99.9%
Percent with VZV Antibody Titer ≥ 5 gpELISA units/mL	84.9%	87.3%	99.5%
Geometric mean titers in gpELISA units/mL (95% CI)	12.0 (11.2, 12.8)	12.8 (11.9, 13.7)	141.5 (132.3, 151.3)

N = Number of subjects vaccinated.

n = Number of subjects included in immunogenicity analysis.

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

Two-Dose Regimen in Adolescents and Adults

In a multicenter study involving susceptible adolescents and adults 13 years of age and older, 2 doses of VARIVAX administered subcutaneously 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 subcutaneously 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.

14.3 Persistence of Immune Response

One-Dose Regimen in Children

In clinical studies involving healthy children who received 1 dose of VARIVAX subcutaneously, 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, 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 administered subcutaneously over 9 years of follow-up, the geometric mean titers (GMTs) 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

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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 VARIVAX subcutaneously, 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 in these studies.

14.4 Studies with Other Vaccines

Concomitant Administration with M-M-R II

In combined clinical studies involving 1080 children 12 to 36 months of age, 653 children received VARIVAX and M-M-R II administered subcutaneously and concomitantly at separate injection sites and 427 received the vaccines six weeks apart. Seroconversion rates and antibody levels to measles, mumps, rubella, and varicella were comparable between the two groups at approximately six weeks postvaccination.

Concomitant Administration with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine

Adsorbed (DTaP) and Oral Poliovirus Vaccine (OPV)

In a clinical study involving 318 children 12 months to 42 months of age, 160 received an investigational varicella-containing vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) administered subcutaneously and concomitantly with booster doses of DTaP and OPV (no longer licensed in the United States). The comparator group of 144 children received M-M-R II concomitantly with booster doses of DTaP and OPV followed by VARIVAX administered subcutaneously six 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. 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.

Concomitant Administration with PedvaxHIB

In a clinical study involving 307 children 12 to 18 months of age, 150 received an investigational varicella-containing vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) administered subcutaneously and 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 administered subcutaneously 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and VZV, and GMTs for PedvaxHIB were comparable between the two groups. 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.

Concomitant Administration with M-M-R II and COMVAX

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] (no longer licensed in the US), M-M-R II, and VARIVAX concomitantly at separate injection sites, and 412 received COMVAX followed by M-M-R II and VARIVAX given concomitantly at separate injection sites, 6 weeks later. In this study VARIVAX was administered subcutaneously. At 6 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 6 weeks later by M-M-R II and VARIVAX with respect to all antigens administered. There were no clinically important differences in reaction rates when the three vaccines were administered concomitantly versus six weeks apart.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4979/4309 — Refrigerator-stable VARIVAX is supplied as follows:

- (1) a single-dose vial of lyophilized vaccine (package A)
- (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)

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نشرة معتمدة: ٤٠٥٥/٤٣٠٩
تاريخ: ٢٠١٧/١٢/٢٠

Not all pack sizes may be marketed.

Vaccine Vial

Before reconstitution, refrigerator-stable VARIVAX has a shelf-life of 24 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.**

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

The vial of diluent should be stored separately at room temperature (Store below 30°C), or in the refrigerator (2° to 8° C), do not Freeze.

Discuss the following with the patient:

- Question the patient, parent, or guardian about reactions to previous vaccines.
- Inform patient, parent, or guardian that vaccination with VARIVAX may not result in protection of all healthy, susceptible children, adolescents, and adults.
- Inform female patients to avoid pregnancy for three months following vaccination.
- Inform patient, parent, or guardian of the benefits and risks of VARIVAX.
- Instruct patient, parent, or guardian to report any adverse reactions or any symptoms of concern to their healthcare professional.

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For patent information: www.merck.com/product/patent/home.html

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Revised: 02/2023

(THIS IS A MEDICAMENT)

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists