PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

VARIVAX® III

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

Lyophilized powder for subcutaneous or intramuscular injection

1350 plaque forming units (PFU) per 0.5 mL single dose vials of Oka/Merck varicella virus, live, attenuated

Active immunizing agent against varicella

ATC code: J07BK01

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

VARIVAX® III is indicated for vaccination against varicella in individuals 12 months of age and older.

1.1 Pediatrics (Less than 1 year old)

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

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

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

- Individuals with a history of hypersensitivity to any component of the vaccine, including gelatin. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Individuals with a history of anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin).

- Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

- Individuals receiving immunosuppressive therapy (including high-dose corticosteroids); however, VARIVAX® III is not contraindicated for use with topical corticosteroids or low-dose corticosteroids, as are commonly used for asthma prophylaxis. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Vaccination with live attenuated varicella vaccine can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids.

- Individuals with primary and acquired immunodeficiency states, including immunosuppression in association with AIDS or other clinical manifestations of infection with human immunodeficiency virus, except immunosuppression in asymptomatic children with CD4 T-lymphocyte percentages ≥ 25%.

- Individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

- Individuals with active untreated tuberculosis.

- Individuals with any active febrile illness with fever > 38.5°C; however, low-grade fever itself is not a contraindication to vaccination.

- Women who are pregnant; the possible effects of the vaccine on fetal development are unknown at this time. However, wild-type varicella is known to sometimes cause fetal harm. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Pediatrics

Children 12 months to 12 years of age should receive an approximately 0.5 mL dose administered intramuscularly or subcutaneously. If a second dose is administered, there should be a minimum interval of 3 months between doses.

Adolescents/Adults

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

4.3 Reconstitution

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

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

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

To reconstitute the vaccine, first withdraw 0.7 mL of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly.

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

Withdraw the entire contents into a syringe and inject the total volume (approximately 0.5 mL) of reconstituted vaccine intramuscularly or subcutaneously, preferably into the outer aspect of the upper arm (deltoid) or the anterolateral thigh. **To minimize loss of potency, it is recommended that the vaccine be administered immediately after reconstitution. Discard if reconstituted vaccine is not used within 90 minutes. Do not refreeze reconstituted vaccine.**

Table 1 - Reconstitution of VARIVAX® III

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
3 mL	Entire contents (approximately 0.7 mL)	0.5 mL	Lyophilized powder reconstituted for injection. Each 0.5 mL dose contains a minimum of 1350 PFU[§] (plaque-forming units) of Oka/Merck varicella virus.
[§] Minimum potency remaining at expiry 90 minutes after reconstitution and storage at room temperature.			

4.4 Administration

FOR INTRAMUSCULAR OR SUBCUTANEOUS ADMINISTRATION.

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

Do not inject intravenously.

VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) is recommended for intramuscular or subcutaneous administration. During clinical trials, some children received varicella vaccine (Oka/Merck) intramuscularly resulting in seroconversion rates similar to those in children who received the vaccine by the subcutaneous route. Persistence of antibody and efficacy in those receiving intramuscular injections have not been defined.

5 OVERDOSAGE

There are no data with regard to overdose.

For management of a suspected vaccine overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular Subcutaneous injection	Lyophilized powder reconstituted for injection. Each 0.5 mL dose contains a minimum of 1350 PFU§ (plaque-forming units) of Oka/Merck varicella virus.	Hydrolyzed gelatin Monosodium L-glutamate Potassium chloride Potassium phosphate monobasic Sodium chloride Sodium phosphate dibasic Sucrose Urea Water for injection
§ Minimum potency remaining at expiry 90 minutes after reconstitution and storage at room temperature.		

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

The diluent (STERILE DILUENT For Merck Sharp & Dohme LLC live, attenuated, virus vaccines) is a sterile, clear, colourless fluid supplied separately in a single-dose vial.

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

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

Active Ingredients

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

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

Other Ingredients

Excipients

Sucrose	17 mg
Hydrolyzed gelatin	8.3 mg
Urea	3.5 mg
Sodium chloride	2.1 mg

Monosodium L-glutamate	0.33 mg
Sodium phosphate dibasic	0.30 mg
Potassium phosphate monobasic	53 mcg
Potassium chloride	53 mcg
Water for injection	to volume

The product contains no preservative. The diluent is sterile water for injection.

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

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

The diluent (0.7 mL) is supplied separately in 3 mL single-dose Type I glass vials.
The container closure systems of VARIVAX® III and the diluent are free of latex.
VARIVAX® III is available in packages of 1 and 10 single-dose vials.
The diluent is also available in packages of 1 and 10 single-dose vials.

7 WARNINGS AND PRECAUTIONS

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

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

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

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

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from fainting.

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

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

- immunocompromised individuals
- pregnant women without documented history of varicella or laboratory evidence of prior infection
- newborn infants of mothers without documented history of varicella or laboratory evidence of prior infection

Reproductive Health: Female and Male Potential
In females of childbearing age, pregnancy should be avoided for 3 months following vaccination (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women).

- **Fertility**
  VARIVAX® III has not been evaluated for its potential to impair fertility.
- **Teratogenic Risk**

  The possible effects of the vaccine on fetal development are unknown (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies in pregnant women. It is not known whether VARIVAX® III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, VARIVAX® III should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see 2 CONTRAINDICATIONS).

A unique Oka/Merck Pregnancy Registry has been in place since 1995; however, it has been discontinued. Reporting to the Registry was voluntary. As of March 2011, 811 women with pregnancy outcome information available for analysis were prospectively enrolled in the Pregnancy Registry for varicella vaccine (Oka/Merck). Of the 170 seronegative women and 627 women of unknown serostatus who received varicella vaccine during pregnancy or within 3 months before pregnancy, none had newborns with abnormalities compatible with congenital varicella syndrome. However, the numbers of exposures are limited and cannot rule out the theoretical risk for congenital varicella syndrome among seronegative women exposed during the high risk period of pregnancy for congenital varicella syndrome (1st or 2nd trimester).

Pregnant women exposed to VARIVAX® III during pregnancy or within 3 months prior to conception are encouraged to report their exposure or suspected adverse reactions by contacting Merck Canada Inc., at 1-800-567-2594 or the Vaccine Safety Section at Public Health Agency of Canada (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php).

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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

The safety and efficacy of VARIVAX® III have not been established in children and young adults who are known to be infected with human immunodeficiency viruses with and without evidence of immunosuppression (see 2 CONTRAINDICATIONS).

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In clinical trials, varicella vaccine (Oka/Merck) was administered subcutaneously to over 17,000 healthy children, adolescents, and adults. Varicella vaccine (Oka/Merck) was generally well tolerated.

In a double-blind, placebo-controlled study among 956 healthy children and adolescents, 914 of whom were serologically confirmed to be susceptible to varicella, the only adverse reactions that occurred at a significantly ($p < 0.05$) greater rate in vaccine recipients than in placebo recipients were pain and redness at the injection site and varicella-like rash.

Children 1 to 12 Years of Age

One-Dose Regimen in Children

In clinical trials involving approximately 8900 healthy children monitored for up to 42 days after a single dose of varicella vaccine (Oka/Merck) the frequency of fever, injection-site complaints, or rashes were reported in Table 3.

Table 3 - Fever, Local Reactions or Rashes (%) in Children 1 to 12 Years of Age 0 to 42 Days After Receipt of a Single Dose of Varicella Vaccine (Oka/Merck)

	Varicella Vaccine (Oka/Merck) N (%)	Peak Occurrence in Postvaccination Day
Fever ≥ 39°C oral	N=8824 14.7%	0–42
Injection site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, induration, stiffness)	N=8913 19.3%	0–2
Varicella-like rash (injection site) Median number of lesions	N=8913 3.4% 2	8–19
Varicella-like rash (generalized) Median number of lesions	N=8913 3.8% 5	5–26

In addition, the most frequently (≥ 1%) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, cough, irritability, fatigue, disturbed sleep, 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 varicella vaccine (Oka/Merck); a causal relationship has not been established.

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

Clinical safety of refrigerator-stable varicella vaccine (Oka/Merck) (n=635) was compared with that of the licensed frozen formulation of varicella vaccine (Oka/Merck) (n=323) for 42 days postvaccination in children 12 to 23 months of age. The safety profiles were comparable for the two different formulations. Pain/tenderness/soreness and erythema were the most commonly reported local reactions. The most common systemic adverse events (reported by ≥10% of subjects, irrespective of causality) were reported in decreasing order of frequency as follows: fever 38.9°C oral; upper respiratory infection; otitis media; cough; rhinorrhea and irritability. Six subjects reported serious adverse events.

Two-Dose Regimen in Children

In a clinical trial, 981 children 12 months to 12 years of age received 2 doses of varicella vaccine (Oka/Merck) 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 (n=1098). The overall incidence of injection-site clinical complaints (primarily erythema, soreness and swelling) observed in the first 4 days following vaccination was 21,7% and 25,4% Postdose 1 and 2, respectively. Among the systemic clinical complaints reported in the 42 day follow up period, upper respiratory

illness occurred with a frequency of 67.3% and 41.3% Postdose 1 and 2, respectively and fatigue occurred with a frequency of 31.4% and 21.2% Postdose 1 and 2, respectively.

Adolescents 13 Years of Age and Older and Adults

In clinical trials involving approximately 1600 healthy adolescents and adults, the majority of whom received two doses of varicella vaccine (Oka/Merck) and were monitored for up to 42 days after any dose, the frequency of fever, injection-site complaints, or rashes were reported in Table 4.

Table 4 - Fever, Local Reactions or Rashes (%) in Adolescents and Adults 0 to 42 Days After Receipt of Varicella Vaccine (Oka/Merck)

	Postdose 1 N (%)	Peak Occurrence in Postvaccination Days	Postdose 2 N (%)	Peak Occurrence in Postvaccination Days
Fever ≥ 37.7˚C oral	N=1584 10.2%	14–27	N=956 9.5%	0–42
Injection site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness)	N=1606 24.4%	0–2	N=955 32.5%	0–2
Varicella-like rash (injection site) Median number of lesions	N=1606 3.1% 2	6–20	N=955 1.0% 2	0–6
Varicella-like rash (generalized) Median number of lesions	N=1606 5.5% 5	7–21	N=955 0.9% 5.5	0–23

In addition, the most frequently (≥ 1%) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, irritability, diarrhea, stiff neck, lymphadenopathy, chills, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, lower respiratory illness, allergic reactions (including allergic rash, hives), and dizziness.

In a randomized open-label clinical trial, 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 measles-like, rubella-like, varicella-like or “other”. Study investigators reviewed the diary card with the participant or participant’s legal guardian 42 days after vaccination to ensure consistency with protocol definitions.

The frequency of solicited adverse reactions based on the final assessment by the investigators is presented in the table below:

Table 5: 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 ≥38.0°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.

Serious adverse events occurred at rates of 0.3% and 1% in the intramuscular and subcutaneous groups, respectively.

Post-Marketing Clinical Studies
In a post-marketing study conducted to evaluate short-term safety (follow-up of 30 or 60 days) in approximately 86,000 children, 12 months to 12 years of age, and in approximately 3600 adolescents, 13 years of age and older, and adults, varicella vaccine (Oka/Merck) was generally well tolerated. No serious vaccine-related adverse events were reported.

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

8.5 Post-Market Adverse Reactions
Since the vaccine has been marketed, the following additional adverse reactions have been reported regardless of causality:

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

Eye Disorders: Necrotizing retinitis (reported only in immunocompromised individuals).

Gastrointestinal Disorders: Nausea; vomiting

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

Infections and Infestations: Varicella (vaccine strain).

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

Respiratory: Pharyngitis; pneumonia/pneumonitis; upper respiratory tract infection.

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

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

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

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

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

9.4 Drug-Drug Interactions

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection (see 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

10 CLINICAL PHARMACOLOGY

Varicella

Varicella is a highly communicable disease in children, adolescents, and adults caused by the varicella-zoster virus (VZV). The disease usually consists of 300 to 500 maculopapular and/or vesicular lesions accompanied by a fever [oral temperature ≥ 37.7°C] in up to 70% of individuals. Although it is generally a benign, self-limiting disease, varicella may be associated with serious complications (e.g., bacterial superinfection, pneumonia, encephalitis, Reye syndrome), and/or death.

10.1 Mechanism of Action

VARIVAX® III 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.

10.2 Pharmacodynamics

Pharmacotherapeutic group: Vaccines, Viral Vaccine; ATC code: J07BK01

10.3 Pharmacokinetics

Duration of Effect

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

Special Populations and Conditions

- **Pediatrics:** VARIVAX® III has not been studied in infants less than 12 months of age and is not recommended for administration in this age group.

11 STORAGE, STABILITY AND DISPOSAL

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

Before reconstitution, VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) has a shelf-life of 24 months and should be stored refrigerated at a temperature of 2°C to 8°C. The vaccine may also be stored in a freezer at temperatures above -50°C; if subsequently transferred to a refrigerator, the vaccine may be placed back in the freezer.

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

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

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

All vaccines must be discarded after the expiration date.

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

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

12 SPECIAL HANDLING INSTRUCTIONS

Discard if reconstituted vaccine is not used within 90 minutes. Do not refreeze reconstituted vaccine.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

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

Product Characteristics:
VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]) is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella virus. When reconstituted as directed, it is a sterile preparation for subcutaneous administration. Each 0.5 mL dose contains a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus when reconstituted and stored at room temperature for 90 minutes. The product contains no preservative.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 6 - Summary of patient demographics for clinical trials with VARIVAX® for active immunization for the prevention of varicella in individuals 12 months of age and older.

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age
051	Multicenter, double-blind (operating under in-house blinding procedures), randomized, controlled	Subjects received one 0.5-mL subcutaneous dose of Process Upgrade Varicella Vaccine (PUVV) (8000 Plaque-Forming Units [PFU]/dose or 25,000 PFU/dose) with the new stabilizer (PGSU) or PUVV (10,000 PFU/dose) with the current stabilizer (PGS), each given concomitantly with a 0.5-mL subcutaneous dose of M-M-R® II.	958	12.8 months
057	Multicenter, double-blind (operating under in-house blinding procedures), randomized, controlled	Subjects received two 0.5-mL subcutaneous doses, approximately 6 weeks apart, of either VARIVAX® manufactured with the 2007 commercial VZV bulk process or VARIVAX® manufactured with the 1999 commercial VZV bulk process, each given concomitantly with a 0.5-mL subcutaneous dose of M-M-R® II.	598	13.0 months

061	Multicenter, double-blind, randomised, controlled, crossover	Subjects received one 0.5-mL subcutaneous dose of VARIVAX® followed by one 0.5-mL subcutaneous dose of M-M-R® II 42 days later Or, Subjects received one 0.5-mL subcutaneous dose of M-M-R® II followed by one 0.5-mL subcutaneous dose of VARIVAX® 42 days later.	507	13.6 months
063	Double-blind (using in-house blinding procedures), randomized, multicenter, comparator-controlled	Subjects received two 0.5-mL subcutaneous doses, approximately 3 months apart, of either VARIVAX™ New Seed Process (NSP) or VARIVAX™ 2007 process, each given concomitantly with a 0.5-mL subcutaneous dose of M-M-R® II.	611	12.9 months
PA03	Randomized, comparator-controlled, multicenter, double-blind	Subjects received two 0.5-mL subcutaneous doses, approximately 3 months apart, of either VARIVAX® Passage Extension 34 (PE34) process or VARIVAX® (2016 commercial product [CP]), each given concomitantly with a 0.5-mL subcutaneous dose of M-M-R® II.	600	13.1 months
V205C-011	Open-label, randomized, comparative, multicenter	Subjects received a 0.5-mL dose of VARIVAX® and a 0.5-mL dose of M-M-R® II concomitantly both by intramuscular (IM) route or both by subcutaneous (SC) route at two separate injection sites.	752	13.7 months

All subjects were healthy children 11 to 23 months of age.

<u>One-Dose Regimen in Children</u>

In combined clinical trials of varicella virus vaccine, live, attenuated (Oka/Merck), hereafter referred to as varicella vaccine (Oka/Merck), at doses ranging from 1000–17,000 PFU, the majority of subjects who received the vaccine and were exposed to wild-type virus were either completely protected from varicella or developed a milder form (for clinical description see below) of the disease.

The protective efficacy of varicella vaccine (Oka/Merck) administered subcutaneously was evaluated in three different ways:

1) by a placebo-controlled, double-blind clinical trial over 2 years (efficacy 95 to 100%); 2) by comparing varicella rates over 7 to 9 years in vaccinees versus historical controls; and 3) by assessment of protection from disease following household exposure over 7 to 9 years.

Although no placebo-controlled trial was carried out with varicella vaccine (Oka/Merck) using the current formulation of the vaccine, a placebo-controlled trial was conducted using a formulation containing 17,000 PFU per dose. In this trial, a single dose of varicella vaccine (Oka/Merck) protected 95 to 100% of children against varicella over a two-year period. The study enrolled healthy individuals 1 to 14 years of age (n = 491 vaccine, n = 465 placebo). In the first year, 8.5% of placebo recipients contracted varicella, while no vaccine recipient did, for a calculated protection rate of 100% during the first varicella season. In the second year, when only a subset of individuals agreed to remain in the blinded study (n = 169 vaccine, n = 163 placebo), 95% protective efficacy was calculated for the vaccine group as compared to placebo.

In early clinical trials, a total of 4240 children received 1000 to 1625 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been followed for up to nine years post single-dose vaccination. In this group there was considerable variation in 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), with an average of 2.5% per year (cumulative event rate of 19.4% by the end of the ninth year). The calculated annual rates in historical control groups, based on one published study are 9.7%, 19.7%, and 11.6% in susceptible subjects who were 1–4, 5–9 and 10–14 years of age, respectively, corresponding to a rate of 14.8% per year in an unvaccinated cohort comparable in age to the vaccinated cohort. 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 9 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 varicella after household exposure compared with the historical attack rate of 87% (388/447 children with no history of varicella) following household exposure to varicella in unvaccinated individuals. The historical rate was derived from one published article. In the 29 subjects in whom varicella occurred postvaccination the disease was generally mild with respect to the number of lesions and no individuals had ≥ 300 lesions.

In later clinical trials, a total of 1114 children 1 to 12 years of age received 2900 to 9000 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been actively followed for up to 10 years post single-dose vaccination. It was observed that 0.2 to 2.3% of vaccinees per year reported varicella (called breakthrough cases), with an average of 0.9% per year (cumulative event rate of 6.7% by the end of the seventh year). The calculated annual rates in historical control groups, based on one published study are 9.7%, 19.7%, and 11.6% in susceptible subjects who were 1–4, 5–9, and 10–14 years of age, respectively, corresponding to a rate of 15.3% per year in an unvaccinated cohort comparable in age to the vaccinated cohort. 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 to10 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) as compared with the historical attack rate of 87% (388/447 children with no history of

varicella) following household exposure to varicella in unvaccinated individuals. The historical rate was derived from one published article.

Among 9202 children ≥ 12 years of age who received 1 injection of varicella vaccine (Oka/Merck), there were 1149 cases of breakthrough varicella (occurring more than 6 weeks postvaccination) of which 20 (1.7%) were classified as severe (≥ 300 lesions and a temperature ≥ 37.8°C oral). By comparison, in a survey of 150 children 1 to 16 years of age, including 92 cases of varicella in previously unvaccinated children and 58 cases of varicella following vaccination, 36% of those unvaccinated had a severe case.

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 varicella vaccine (Oka/Merck) (n=1114) or 2 doses of varicella vaccine (Oka/Merck) (n=1102) given 3 months apart. Subjects were actively followed for varicella, any varicella-like illness, or herpes zoster and any exposures to varicella or herpes zoster on an annual basis for 10 years after vaccination. Persistence of 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. Children who received a 2-dose regimen of varicella vaccine had a lower varicella incidence than 1-dose regimen post-vaccination, observed up to 10 years of follow-up.

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

VARIVAX® III is recommended for subcutaneous administration. However, during clinical trials, some children received varicella vaccine (Oka/Merck) intramuscularly resulting in seroconversion rates similar to those in children who received the vaccine by the subcutaneous route. Persistence of antibody and efficacy in those receiving intramuscular injections have not been defined.

Clinical Data in Adolescents and Adults

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

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

14.2 Immunogenicity

Clinical trials with several formulations of the vaccine containing attenuated virus ranging from 1000 to 50,000 PFU per dose have demonstrated that varicella vaccine (Oka/Merck) induces detectable

humoral immune responses in a high proportion of individuals and is generally well tolerated in healthy individuals ranging from 12 months to 55 years of age.

One-Dose Regimen in Children

Seroconversion as defined by the acquisition of any detectable varicella antibodies (based on assay cut-off that generally corresponds to 0.6 units in the gpELISA, a highly sensitive assay which is not commercially available), was observed in 98% of vaccinees at approximately 4 to 6 weeks postvaccination in 9610 susceptible children 12 months to 12 years of age who received doses ranging from 1000 to 50,000 PFU. The antibody titer determined by gpELISA has been shown to correlate with levels of neutralizing antibody and can therefore be regarded as a clinically relevant marker of functional immunity. An inverse relationship was established between the varicella antibody titer 6 weeks after vaccination and the risk of breakthrough varicella. It can be regarded as an approximate correlate of protection for individual vaccinees. Rates of breakthrough disease were significantly lower among children with varicella antibody titers ≥ 5 gpELISA units compared to children with titers < 5 gpELISA units. Titers ≥ 5 gpELISA units were induced in approximately 83% of children vaccinated with a single dose of vaccine at 1000 to 50,000 PFU per dose. The immune response rate to varicella vaccine (Oka/Merck) (as determined by the percentage of subjects with varicella antibody titers ≥ 5 gpELISA units at 6 weeks postvaccination, an approximate correlate of protection) in subjects participating in follow-up studies ranged from 72 to 98%.

Immunogenicity of refrigerator-stable varicella vaccine (Oka/Merck) (formulations containing attenuated virus ranging from 6650 to 28,400 PFU per dose), was compared with that of the licensed frozen formulation (9189 PFU per dose) in a double-blind, randomized, multicenter study in 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; the antibody responses were comparable across the 3 treatment groups, with the percentage of subjects with varicella antibody titers ≥5 gpELISA units at 6 weeks postvaccination ranging from 93 to 95%.

In an open label clinical trial 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 ≥-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 group.

Two-Dose Regimen in Children

In a multicenter study, 2216 healthy children 12 months to 12 years of age received either 1 dose or two doses of varicella vaccine (Oka/Merck) or administered subcutaneously 3 months apart and 892 and 796 children in dose-1 and dose-2 groups, respectively were included for antibody response assessment 6 weeks after the vaccination. As results, titers ≥5 gpELISA units were induced in

approximately 84.9% and 99.5% of children vaccinated with varicella vaccine at 6 weeks postdose-1 and postdose-2, respectively.

The results from this study in which a second dose of varicella vaccine (Oka/Merck) was administered at least 3 months after the initial dose demonstrate significant boosting of the VZV antibodies.

Two-Dose Regimen in Adolescents and Adults

In a multicenter study involving susceptible adolescents 13 years of age and older and adults, two doses of varicella vaccine (Oka/Merck) administered subcutaneously four to eight weeks apart induced a seroconversion rate (gpELISA ≥ 0.6 units) of approximately 75% in 539 individuals four weeks after the first dose and of 99% in 479 individuals four weeks after the second dose. The average antibody response in vaccinees who received the second dose eight weeks after the first dose was higher than that in those who received the second dose four weeks after the first dose. In another multicenter study involving adolescents and adults, two doses of varicella vaccine (Oka/Merck) administered subcutaneously eight weeks apart induced a seroconversion rate (gpELISA ≥ 0.6 units) of 94% in 142 individuals six weeks after the first dose and 99% in 122 individuals six weeks after the second dose.

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

Persistence of Immune Response

One-Dose Regimen in Children

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

Two-Dose Regimen in Children

In recipients of 1 dose of varicella vaccine (Oka/Merck) 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 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.

Two-Dose Regimen in Adolescents and Adults

In clinical studies involving healthy adolescents and adults who seroconverted after 2 doses of VARIVAX® III subcutaneously, detectable varicella antibodies (gpELISA ≥ 0.6 units) were present in 97.9% (568/580) at 1 year, 97.1% (34/35) at 2 years, 100% (144/144) at 3 years, 97.0% (98/101) at 4 years, 97.5% (78/80) at 5 years, and 100% (45/45) at 6 years postvaccination.

A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella which could account for the apparent long-term persistence of antibody levels after vaccination in these studies. The duration of protection from varicella obtained using varicella vaccine (Oka/Merck) in the absence of wild-type boosting is unknown.

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

Transmission

In the placebo-controlled trial, transmission of vaccine virus was assessed in household settings (during the 8-week 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 Transmission).

Herpes Zoster

Overall, 9543 healthy children (12 months to 12 years of age) and 1652 adolescents (13 years of age and older) and adults have been vaccinated with varicella vaccine (Oka/Merck) in clinical trials. Twelve cases of herpes zoster have been reported in children during 84,414 person years of follow-up in clinical trials, resulting in a calculated incidence of at least 14 cases per 100,000 person years. The completeness of this reporting has not been determined. Two cases of herpes zoster have been reported in the adolescent and adult age group during 12,372 person years of follow-up in clinical trials resulting in a calculated incidence of 16 cases per 100,000 person years.

All 14 cases were mild and no sequelae were reported. Two cultures (one child and one adult) obtained from vesicles were positive for wild-type varicella zoster virus as confirmed by restriction endonuclease analysis. The long-term effect of varicella vaccine (Oka/Merck) on the incidence of herpes zoster, particularly in those vaccinees exposed to wild-type varicella, is unknown at present.

In children, the reported rate of zoster in vaccine recipients appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella.The incidence of zoster in adults who have had wild-type varicella infection is higher than that in children.

Reye Syndrome

Reye syndrome has occurred in children and adolescents following wild-type varicella infection, the majority of whom had received salicylates. In clinical studies in healthy children and adolescents in the United States, physicians advised varicella vaccine recipients not to use salicylates for six weeks after vaccination. There were no reports of Reye syndrome in varicella vaccine recipients during these studies (see 7 WARNINGS AND PRECAUTIONS).

Studies with Other Vaccines

In combined clinical studies involving 1107 children 12 to 36 months of age, 680 children received varicella vaccine (Oka/Merck) and M-M-R® II (measles, mumps and rubella virus vaccine live attenuated, Merck Std.) administered subcutaneously and concomitantly at separate sites and 427

received the vaccines six weeks apart. Seroconversion rates and antibody levels were comparable between the two groups at approximately six weeks postvaccination to each of the virus vaccine components. No differences were noted in adverse reactions reported in those who received varicella vaccine (Oka/Merck) concomitantly with M-M-R® II at separate sites and those who received varicella vaccine (Oka/Merck) and M-M-R® II at different times.

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

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

In a clinical study involving 609 children 12 months to 23 months of age, 305 received varicella vaccine (Oka/Merck), M-M-R® II, and *Haemophilus influenzae* type b, diphtheria, tetanus, and pertussis combined vaccine concomitantly at separate sites and 304 received M-M-R® II and *Haemophilus influenzae* type b, diphtheria, tetanus, and pertussis combined vaccine given concomitantly followed by varicella vaccine (Oka/Merck) 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and varicella were similar between the two groups. Compared to prevaccination GMTs, the six week postvaccination boost in GMTs for *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis was similar between the two groups. GMTs for all antigens were similar except for varicella which was lower when varicella vaccine (Oka/Merck) was administered concomitantly with M-M-R® II and *Haemophilus influenzae* type b, diphtheria, tetanus, and pertussis combined vaccine but within the range of GMTs seen in previous clinical experience when varicella vaccine (Oka/Merck) was administered alone. At 1 year postvaccination, GMTs for measles, mumps, rubella, varicella and *Haemophilus influenzae* type b were similar between the two groups. All three vaccines were well tolerated regardless of whether they were administered concomitantly at separate sites or 6 weeks apart. There were no clinically important differences in reaction rates when the three vaccines were administered concomitantly versus 6 weeks apart.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: VARIVAX® III has not been evaluated for its carcinogenic potential.

Genotoxicity: VARIVAX® III has not been evaluated for its genotoxicity potential.

Reproductive and Developmental Toxicology: VARIVAX® III has not been evaluated for its potential to impair fertility. It is also not known whether VARIVAX® III can cause harm to the fetus when administered to a pregnant woman.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

VARIVAX® III

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

Read this carefully before you or your child is vaccinated with **VARIVAX® III**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VARIVAX® III**.

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

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

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

What are the ingredients in VARIVAX® III?
Medicinal ingredients: Each 0.5 mL dose contains as active ingredient a minimum of 1350 PFU (plaque-forming units) of live attenuated varicella virus (Oka/Merck strain).
Non-medicinal ingredients:
Powder: hydrolyzed gelatin, monosodium L-glutamate, neomycin (trace quantities), potassium chloride, potassium phosphate monobasic, sodium chloride, sodium phosphate dibasic, sucrose, urea,

Diluent: water for injection.

VARIVAX® III comes in the following dosage forms:
VARIVAX® III is supplied as a sterile white powder in a single-dose vial.

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

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

Do not use VARIVAX® III if:
VARIVAX® III should not be used by anyone who:

- is allergic to any of its ingredients (including gelatin and neomycin). A list of ingredients can be found below
- has a blood disorder or any type of cancer that affects their immune system
- is taking medications to suppress their immune system
- has an immune deficiency, including one as a result of a disease (such as AIDS)

- has active untreated tuberculosis
- has a fever > 38.5°C (> 101.3°F)
- is pregnant (in addition, pregnancy should be avoided for 3 months after vaccination)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child gets VARIVAX® III. Talk about any health conditions or problems you or your child may have, including if you or your child:

- has any allergies (especially to gelatin or neomycin)
- has a family member with a weakened immune system

In rare circumstances, it is possible to catch chickenpox, including severe chickenpox, from a person who has been vaccinated with VARIVAX® III. This may occur in persons who have not previously been vaccinated or never had chickenpox, as well as persons who fall into one of the following categories:

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

Whenever possible, individuals who have been vaccinated with VARIVAX® III should attempt to avoid close contact, for up to 6 weeks following the vaccination, with anyone who falls into one of the categories above. Tell your doctor if there is anyone who falls into one of the categories above and is expected to be in close contact with the person being vaccinated.

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

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

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

Other warnings you should know about:
As with other vaccines, VARIVAX® III may not fully protect all those who receive it.

Tell your healthcare professional about all the medicines you or your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VARIVAX® III:

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

- Vaccination should be deferred for at least 5 months after any blood or plasma transfusions, or administration of immune globulin or varicella zoster immune globulin (VZIG).
- Following vaccination with VARIVAX® III, you or your child should not receive any immune globulin, including VZIG, for 2 months thereafter, unless your doctor decides it is necessary.
- VARIVAX® III can be given at the same time as measles, mumps and rubella vaccine (M-M-R® II) and vaccines against Haemophilus influenzae type b, diphtheria, tetanus and pertussis (whooping cough). If VARIVAX® III is not given at the same time as M-M-R® II a 1-month interval between these 2 vaccines should be observed. Your doctor will decide the vaccination schedule.

How to take VARIVAX® III:

- VARIVAX® III will be given to you or your child by a healthcare professional in a healthcare setting

Usual dose:

- VARIVAX® III is given by intramuscular or subcutaneous injection as follows:
    - Children 12 months to 12 years of age should receive a 0.5 mL dose. The dose of the vaccine is the same for everyone. If your child is 12 months to 12 years old and your doctor gives a second dose, the second dose should be given at least 3 months after the first dose.
    - Adolescents 13 years of age and older and adults should receive two doses. The second dose should be given 4 to 8 weeks after the first dose.

See your doctor for more details.

Overdose:

If you think you, or a person you are caring for, have received too much VARIVAX® III, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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

What are possible side effects from using VARIVAX® III?
These are not all the possible side effects you or your child may have when receiving VARIVAX® III. If you or your child experience any side effects not listed here, tell your healthcare professional.

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

Other side effects such as nausea, vomiting, and chickenpox have been reported. Some reported side effects were serious, including allergic reactions (in individuals with or without an allergic history); bruising more easily than normal; red or purple, flat, pinhead spots under the skin; severe paleness;

difficulty walking; severe skin disorders; and skin infection. Rarely, inflammation of the brain (encephalitis)†, stroke (cerebrovascular accident), inflammation of the coverings of the brain and spinal cord (meningitis)†, inflammation of the lung (pneumonia/pneumonitis) and seizures with or without a fever have been reported. The relationship of these rare side effects to the vaccine has not been established.

†Can be from naturally occurring chickenpox or the vaccine in healthy individuals or individuals with lowered immunity.

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

If you or your child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with his daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.
Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Merck Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

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

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

All vaccines must be discarded after the expiration date.

Keep out of reach and sight of children.

If you want more information about VARIVAX® III:
- Talk to your healthcare professional.

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.merck.ca, or by calling at 1-800-567-2594.

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