SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VARICELLA VACCINE LIVE I.P.
(Oka/Merck)
Powder and Solvent for suspension for injection
0.5mL Single Dose Vial of powder and single dose sterile diluent syringe/vial (WFI)
Brand Name: VARIPED®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients

VARIPED® when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.5 mL dose contains: a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus when reconstituted and stored at room temperature for 30 minutes.

Inactive Ingredients

Each 0.5 mL dose contains: approximately 18 mg of sucrose, 8.9 mg of hydrolyzed gelatin, 3.6 mg of urea, 2.3 mg of sodium chloride, 0.36 mg of monosodium L glutamate, 0.33 mg of sodium phosphate dibasic, 57 mcg of potassium phosphate monobasic, 57 mcg of potassium chloride. The product also contains residual components of MRC 5 cells and trace quantities of neomycin and bovine calf serum from MRC 5 culture media. The product contains no preservative.

3. PHARMACEUTICAL FORM

VARIPED® is supplied as Powder and Solvent for suspension for subcutaneous injection.
White to off-white powder and clear, colorless liquid solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VARIPED® is indicated for active immunization for prevention of varicella in individuals from 12 months of age and older.

4.2 Posology and method of administration

Posology:

FOR SUBCUTANEOUS ADMINISTRATION. Do not inject intravenously.

VARIPED is administered as an approximately 0.5mL dose by subcutaneous injection into the outer aspect of the upper arm (deltoid region) or the anterolateral thigh.

Children (12 months to 12 years of age)

If a second dose is administered, there should be a minimum interval of 3 months between doses *[see clinical studies]*.

Adolescents (≥ 13 years of age) and Adults

Two doses of vaccine, to be administered with a minimum interval of 4 weeks between doses *[see clinical studies]*.

Methods of Administration

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

Do not freeze reconstituted vaccine.

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

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

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

Do not freeze reconstituted vaccine.

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

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

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

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

4.3 Contraindications
History of hypersensitivity to any component of the vaccine, including gelatin.

History of anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin).

Blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Immunosuppressive therapy (including high-dose corticosteroids); however, VARIPED® 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.

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%.

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

Active untreated tuberculosis.

Any active febrile illness with fever >38.5°C (>101.3°F); however, low-grade fever itself is not a contraindication to vaccination.

Pregnancy and Lactation; 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 section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

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 VARIPED® is unknown.

The safety and efficacy of VARIPED® have not been established in children and young adults who are known to be infected with human immunodeficiency virus with and without evidence of immunosuppression (see also section 4.3 CONTRAINDICATIONS).

Transmission

Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella like rash and healthy susceptible contacts. Transmission of vaccine virus from vaccinees who do not develop a varicella like rash has also been reported.

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

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

4.5 Interaction with other medicinal products and other forms of Interaction

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 VARIPED®, any immune globulin including VZIG should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination.

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIPED® as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection.

Use with Other Vaccines

Results from clinical studies indicate that VARIPED® can be administered concomitantly with M M R* II (Measles, Mumps, and Rubella Virus Vaccine Live), TETRAMUNE** (diphtheria and tetanus toxoids and pertussis vaccine adsorbed and Haemophilus b conjugate vaccine), or COMVAX* (Haemophilus influenzae type b conjugate and hepatitis B vaccine). If VARIPED® is not given concomitantly with M M R II, a 1 month interval between the 2 live virus vaccines should be observed.

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

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4.6 Pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies in pregnant women. It is not known whether VARIPED® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, VARIPED® should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see section 4.3 CONTRAINDICATIONS).

Nursing Mothers

It is not known whether varicella vaccine virus is secreted in human milk. Therefore, because some viruses are secreted in human milk, caution should be exercised if VARIPED® (Refrigerated) is administered to a nursing woman (see section 4.3 CONTRAINDICATIONS).

Pediatric Use

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Studies

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

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

In clinical trials involving 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 as follows:

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

Reaction	N	Post Dose 1	Peak Occurrence in Postvaccination Days
Fever ≥102°F (38.9°C) Oral	8824	14.7%	0-42
Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, induration, stiffness)	8913	19.3%	0-2
Varicella-like rash (injection site) Median number of lesions	8913	3.4% 2	8-19
Varicella-like rash (generalized) Median number of lesions	8913	3.8% 5	5-26

In addition, the most frequently (³1%) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, cough, irritability/nervousness, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, diaper rash/contact rash, headache, teething, malaise, abdominal pain, other rash, nausea, eye complaints, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions (including allergic rash, hives), stiff neck, heat rash/prickly heat, insect bites, arthralgia, eczema/dry skin/dermatitis, constipation, itching.

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

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

Adolescents and Adults 13 Years of Age and Older
In clinical trials involving 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 as follows:

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

Reaction	N	Post Dose 1	Peak Occurrence in Postvaccination Days	N	Post Dose 2	Peak Occurrence in Postvaccination Days
Fever ≥100°F (37.8°C) Oral	1584	10.2%	14-27	956	9.5%	0-42
Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness)	1606	24.4%	0-2	955	32.5%	0-2
Varicella-like rash (injection site) Median number of lesions	1606	3.1% 2	6-20	955	1.0% 2	0-6
Varicella-like rash (generalized) Median number of lesions	1606	5.5% 5	7-21	955	0.9% 5.5	0-23

In addition, the most frequently (³1%) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, irritability/nervousness, diarrhea, stiff neck, lymphadenopathy, chills, eye complaints, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, constipation, lower respiratory illness, allergic reactions (including allergic rash, hives), contact rash, cold/canker sore, dizziness, and insect bites.

Post-Marketed Clinical Studies

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

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

Post-Marketed Experience

The following additional side effects have been reported regardless of causality since the vaccine has been marketed:

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

Infections and Infestations: Varicella (vaccine strain).

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

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

4.9 Overdose
There are no data with regard to overdose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: virus vaccines - varicella viruses; ATC code: J07BK01

Clinical Studies
Evaluation of Clinical Efficacy Afforded by VARIPED®
Clinical Data in Children
In combined clinical trials of varicella virus vaccine live (Oka/Merck) [hereafter referred to as varicella vaccine (Oka/Merck)] at doses ranging from 1,000 to 17,000 PFU, the majority of subjects who received varicella vaccine (Oka/Merck) and were exposed to wild-type virus were either completely protected from chickenpox or developed a milder form (for clinical description see below) of the disease.

The protective efficacy of varicella vaccine (Oka/Merck) was evaluated in three different ways: 1) by a placebo-controlled, double-blind clinical trial over 2 years (efficacy 95 to 100%); 2) by comparing chickenpox rates over 7 to 9 years in vaccinees versus historical controls (efficacy 83 to 94%); and 3) by assessment of protection from disease following household exposure over 7 to 9 years (efficacy 81 to 88%).

Although no placebo-controlled trial was carried out with VARIPED® 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 chickenpox over a two-year period. The study enrolled healthy individuals 1 to 14 years of age (n=491 vaccine, n=465 placebo). In the first year, 8.5% of placebo recipients contracted chickenpox, while no vaccine recipient did, for a calculated protection rate of 100% during the first varicella season. In the second year, when only a subset of individuals agreed to remain in the blinded study (n=169 vaccine, n=163 placebo), 95% protective efficacy was calculated for the vaccine group as compared with 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 varicella vaccine (Oka/Merck) and have been followed for up to 9 years post single-dose vaccination. In this group, there was considerable variation in chickenpox rates among studies and study sites, and much of the reported data was acquired by passive follow-up. It was observed that 0.3 to 3.8% of vaccinees per year reported chickenpox (called breakthrough cases). This represents an approximate 83% (95% confidence interval [CI], 82%, 84%) decrease from the age-adjusted expected incidence rates in susceptible subjects over this same period. In those who developed breakthrough chickenpox postvaccination, the majority experienced mild disease (median of the maximum number of lesions <50). In one study, a total of 47% (27/58) of breakthrough cases had <50 lesions compared with 8% (7/92) in unvaccinated individuals, and 7% (4/58) of breakthrough cases had ≥300 lesions compared with 50% (46/92) in unvaccinated individuals.

Among a subset of vaccinees who were actively followed in these early trials for up to 9 years postvaccination, 179 individuals had household exposure to chickenpox. There were no reports of breakthrough chickenpox in 84% (150/179) of exposed children, while 16% (29/179) reported a mild form of chickenpox (38% (11/29) of the cases with a maximum total number of <50 lesions; no individuals with ≥300 lesions). This represents an 81% reduction in the expected number of varicella cases utilizing the historical attack rate of 87% following household exposure to chickenpox in unvaccinated individuals in the calculation of efficacy.

In later clinical trials, a total of 1164 children 1 to 12 years of age received 2900 to 9000 PFU of attenuated virus per dose of varicella vaccine (Oka/Merck) and have been actively followed for up to 7 years post single-dose vaccination. It was observed that 0.2 to 2.3% of vaccinees per year reported breakthrough chickenpox for up to 7 years post single-dose vaccination. This represents an approximate 94% (95% CI, 92%, 95%) decrease from the age-adjusted expected incidence rates in susceptible subjects over the same period. In those who developed breakthrough chickenpox postvaccination, the majority experienced mild disease with the median of the maximum total number of lesions <50. The severity of reported breakthrough chickenpox, as measured by number of lesions and maximum temperature, appeared not to increase with time since vaccination.

Among a subset of vaccinees who were actively followed in these later trials for up to 7 years postvaccination, 80 individuals were exposed to an unvaccinated individual with wild-type chickenpox in a household setting. There were no reports of breakthrough chickenpox in 90% (72/80) of exposed children, while 10% (8/80) reported varicella after household exposure. This represents an 88% reduction in the expected number of varicella cases utilizing the historical attack rate of 87% following household exposure to chickenpox in unvaccinated individuals in the calculation of efficacy. The reported cases of varicella were mild, with annual median number of lesions (maximum daily total) ranging from 10 to 34.

Among 9202 children ≤12 years of age who received 1 injection of varicella vaccine (Oka/Merck), there were 1149 cases of breakthrough varicella (occurring more than 6 weeks postvaccination) of which 20 (1.7%) were classified as severe (≥300 lesions and a temperature ≥37.8°C oral). Compared with the proportion of severe cases (36%) from wild-type varicella infection in unvaccinated historical controls, this represents a 95% relative reduction in the proportion of severe cases among recipients of varicella vaccine who developed breakthrough varicella.

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

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).

Immunogenicity of Varicella Vaccine (Oka/Merck)

Clinical trials with several formulations of the vaccine containing attenuated virus ranging from 1000 to 50,000 PFU per dose have demonstrated that varicella vaccine (Oka/Merck) induces detectable humoral immune responses in a high proportion of individuals and is generally well tolerated in healthy individuals ranging from 12 months to 55 years of age.

Seroconversion as defined by the acquisition of any detectable varicella antibodies (based on assay cutoff that generally corresponds to 0.6 units in the gpELISA, a highly sensitive assay which is not commercially available), was observed in 98% of vaccinees at approximately 4 to 6 weeks postvaccination in 9610 susceptible children 12 months to 12 years of age who received doses ranging from 1000 to 50,000 PFU. 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 correlation of protection) in subjects participating in follow-up studies ranged from 72 to 98%.

Two-Dose Regimen in Adolescents and Adults

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

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

Persistence of Immune Response

In those clinical studies involving healthy children who have been followed long-term post single-dose vaccination, detectable varicella antibodies (gpELISA ≥0.6 units) were present in 99.1% (3092/3120) at 1 year, 99.4% (1382/1391) at 2 years, 98.7% (1032/1046) at 3 years, 99.3% (997/1004) at 4 years, 99.2% (727/733) at 5 years, and 100% (432/432) at 6 years postvaccination.

Two-Dose Regimen in Adolescents and Adults

In clinical studies involving healthy adolescents and adults who received 2 doses of vaccine, detectable varicella antibodies (gpELISA ≥0.6 units) were present in 97.9% (568/580) at 1 year, 97.1% (34/35) at 2 years, 100% (144/144) at 3 years, 97.0% (98/101) at 4 years, 97.4% (76/80) at 5 years, and 100% (34/34) at 6 years postvaccination.

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

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

Transmission

In the placebo-controlled trial, transmission of vaccine virus was assessed in household settings (during the 8-week postvaccination period) in 416 susceptible placebo recipients who were household contacts of 445 vaccine recipients. Of the 416 placebo recipients, three developed chickenpox and seroconverted, nine reported a varicella-like rash and did not seroconvert, and six had no rash but seroconverted. If vaccine virus transmission occurred, it did so at a very low rate and possibly without recognizable clinical disease in contacts. These cases may represent either wild-type varicella from community contacts or a low incidence of transmission of vaccine virus from vaccinated contacts (see WARNINGS AND PRECAUTIONS, *Transmission*). Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from vaccinees who do not develop a varicella-like rash has also been reported.

Herpes Zoster

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

All 14 cases of herpes zoster 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.

Studies with Other Vaccines

In combined clinical studies involving 1107 children 12 to 36 months of age, 680 received varicella vaccine (Oka/Merck) and M-M-R II* (Measles, Mumps, and Rubella Virus Vaccine Live) 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 (see section 4.5 Interaction with other medicinal products and other forms of Interaction).

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

In another clinical study involving 306 children 12 to 18 months of age, 151 received an investigational vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with a booster dose of PedvaxHIB* [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] while 155 received M-M-R II concomitantly with a booster dose of PedvaxHIB followed by varicella vaccine (Oka/Merck) 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and varicella, and geometric mean titers for PedvaxHIB were comparable between the two groups, but anti-varicella 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.

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

In a clinical study involving 822 children 12 to 15 months of age, 410 received COMVAX* [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) vaccine], M-M-R II, and varicella vaccine (Oka/Merck) concomitantly at separate sites, and 412 received COMVAX followed by M-M-R II and varicella vaccine (Oka/Merck) given concomitantly at separate sites, 6 weeks later. At 6 weeks postvaccination, the immune responses for the subjects who received the concomitant injections of COMVAX, M-M-R II, and varicella vaccine (Oka/Merck) were similar to those of the subjects who

received COMVAX followed 6 weeks later by M-M-R II and varicella vaccine (Oka/Merck) with respect to all antigens administered. All 3 vaccines were generally well tolerated regardless of whether they were administered concomitantly at separate sites or 6 weeks apart. There were no clinically important differences in reaction rates when the 3 vaccines were administered concomitantly versus 6 weeks apart.

VARIPED® 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.

5.2 Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data
Traditional preclinical safety studies were not performed, but there are no preclinical concerns considered relevant to clinical safety beyond data included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Powder:
Sucrose
Hydrolysed gelatin
Urea
Sodium chloride
Monosodium L-glutamate
Anhydrous disodium phosphate
Potassium dihydrogen phosphate
Potassium chloride

Solvent:
Water for Injections

6.2 Incompatibilities
The vaccine must not be mixed with other medicinal products.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Combination pack with vaccine vial and diluent
For combination packs with vaccine vial and diluent packaged together, store in the refrigerator at 2 to 8°C (36 to 46°F). DO NOT STORE THE COMBINATION PACK IN THE FREEZER.

Before reconstitution, VARIPED® 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.

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

6.5 Nature and contents of container

The product is available in a pack of single dose vial and solvent (either filled syringe diluent or vial diluent).
The solvent provided is a prefilled syringe of water for injections with a fixed needle or without a needle.
The secondary packaging for the without needle presentation may also contain 2 separate needles.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION/ PREQUALIFICATION HOLDER

MSD Pharmaceuticals Pvt. Ltd.,
Gala No. 1B, Building No. B-3,
City Link Warehouses Complex,
Mumbai Nashik Highway, Vadapa, Bhiwandi,
Thane 421302, Maharashtra, INDIA

8. MARKETING>AUTHORISATION NUMBER(S)

Import Permission No.: Import-148/14

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45): 03 July 2014

Manufactured and packed by	Imported and Marketed by
Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN, Haarlem The Netherlands	MSD Pharmaceuticals Pvt. Ltd., Gala No. 1B, Building No. B-3, City Link Warehouses Complex, Mumbai Nashik Highway, Vadapa, Bhiwandi, Thane 421302, Maharashtra, INDIA

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