SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ONVARA lyophilised powder and solvent for suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,5 ml dose contains: a minimum of 1 350 PFU (plaque forming units) of Oka/Merck (live, attenuated) varicella virus when reconstituted.

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.

ONVARA contains sucrose.

Excipients:

For the full list of excipients, see section **6.1**.

3 PHARMACEUTICAL FORM

Powder

Lyophilised, white, compact crystalline pellet

Reconstituted vaccine suspension

ONVARA, when reconstituted, is a clear, colourless to pale yellow liquid, free from visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ONVARA is indicated for vaccination against varicella in individuals from 12 months of age and older.

4.2 Posology and method of administration

FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravenously.

Children (12 months to 12 years of age) should receive a 0,5 ml dose administered subcutaneously.

Adolescents (13 years of age and older) and adults should receive a 0,5 ml dose administered subcutaneously.

If a second dose is administered, children (12 months to 12 years of age) should receive the second dose at least 3 months following the initial dose. For those 13 years of age and older, the second dose should be administered 4 to 8 weeks after the initial dose.

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

Method of administration

The diluent should be stored separately at room temperature (20 to 25 °C), 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.

Do not remove the syringe that has been used to inject the diluent into the vial of ONVARA as the reconstituted ONVARA will be withdrawn with the same syringe for administration to the patient.

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.

4.3 Contraindications

History of hypersensitivity to any component of the vaccine, including gelatine.

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

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

Immunosuppressive therapy (including high-dose corticosteroids); however, ONVARA 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 $\geq$ 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 (refer to section **4.6**)

4.4 Special warnings and precautions for use

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

The duration of protection from varicella infection after vaccination with ONVARA is unknown.

The safety and efficacy of ONVARA 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**).

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.

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 ONVARA, 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 ONVARA (Refrigerated) as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection.

Concomitant administration with other vaccines

ONVARA has been administered to toddlers at the same time as, but at a different injection site from, a combined measles, mumps, and rubella vaccine, *Haemophilus influenzae* type b conjugate combined vaccine, or *Haemophilus influenzae* type b

Conjugate (Meningococcal Protein Conjugate), Hepatitis B (Recombinant)

combined vaccine, diphtheria/tetanus/whole-cell pertussis vaccine, and oral polio virus vaccine. There was no evidence of a clinically relevant difference in the immune responses to any of the antigens when co-administered with ONVARA. If varicella vaccine (live) (Oka/Merck strain) is not given concomitantly with measles, mumps, and rubella virus vaccine live, a 1-month interval between the 2 live virus vaccines should be observed.

Concurrent administration of ONVARA and tetravalent, pentavalent or hexavalent (diphtheria, tetanus, and acellular pertussis [DTaP])-based vaccines has not been evaluated.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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 ONVARA (Refrigerated) is administered to a nursing woman.

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

Summary of the safety profile

Clinical Studies

In clinical trials, varicella vaccine (Oka/Merck), was administered to over 15 000 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 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 was 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	8 824	14.7 %	0-42
Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, induration, stiffness)	8 913	19.3 %	0-2

Varicella-like rash (injection site) Median number of lesions	8 913	3.4 % 2	8-19
Varicella-like rash (generalized) Median number of lesions	8 913	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/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.

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 ≥102.0 °F (38.9 °C) oral; upper respiratory infection; otitis media; cough; rhinorrhoea and irritability. Six subjects reported serious adverse events.

Two-Dose Regimen in Children

In a clinical trial, 981 children 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. The overall incidence of injection-site clinical complaints (primarily erythema and swelling) observed in the first 4 days following vaccination was 25.4 % Postdose 2 and 21.7 % Postdose 1, whereas the overall incidence of systemic clinical complaints in the 42-day follow-up period was lower Postdose 2 (66.3 %) than Postdose 1 (85.8 %).

Adolescents 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 was 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 Postvaccin-ation Days	N	Post Dose 2	Peak Occurrence in Postvaccin-ation Days
Fever ≥100°F (37.8°C) Oral	1 584	10.2 %	14-27	956	9.5 %	0-42
Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness)	1 606	24.4 %	0-2	955	32.5 %	0-2
Varicella-like rash (injection site) Median number of lesions	1 606	3.1 % 2	6-20	955	1.0 % 2	0-6
Varicella-like rash (generalized)	1 606	5.5 %	7-21	955	0.9 %	0-23

Median number of lesions		5			5.5	

In addition, the most frequently (≥ 1 %) reported adverse experiences, without regard to causality, are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, irritability/nervousness, diarrhoea, 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 3 600 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-marketing 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 oedema, facial oedema, and peripheral oedema; 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 anaemia; 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; meningitis†; dizziness; paresthesia; irritability.

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 impetigo and cellulitis; herpes zoster.

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

4.9 Overdose

There are no data with regard to overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.30.2 Antigens

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

Mechanism of Action

ONVARA 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.

Transmission

In the placebo-controlled efficacy trial, transmission of vaccine virus was assessed in household settings (during the 8-week post-vaccination 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 healthy 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 **Special warnings and precautions for use**, Transmission). Transmission of vaccine virus from a mother who did not develop a varicella-like rash to her newborn infant has also been reported.

Herpes Zoster

Overall, 9 543 healthy children (12 months to 12 years of age) and 1 652 adolescents and adults (13 years of age and older) have been vaccinated with ONVARA 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 has 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 without sequelae. Two cultures (one child and one adult) obtained from vesicles were positive for wild-type VZV as confirmed by restriction endonuclease analysis. The long-term effect of 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 herpes zoster in vaccine recipients appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella. The incidence of herpes zoster in adults who have had wild-type varicella infection is higher than that in children.

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.

Duration of Protection

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

Clinical Studies

Evaluation of Clinical Efficacy

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 varicella or developed a milder form of the disease.

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

1) by a double-blind, placebo-controlled trial over 2 years efficacy 95 to 100 %);
2) by comparing varicella 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 varicella vaccine 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 with placebo.

In early clinical trials, a total of 4 240 children 1 to 12 years of age received 1 000 to 1 625 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 varicella 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 varicella (called breakthrough cases). This represents an approximate 83 % (95 % confidence interval [CI], 82 %, 84 %) decrease from the age-adjusted expected incidence rates in susceptible subjects over this same period. In those who developed breakthrough varicella post-vaccination, 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 post-vaccination, 179 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 84 % (150/179) of exposed children, while 16 % (29/179) reported a mild form of varicella (38 % [11/29] of the cases with a maximum total number of <50 lesions; no individuals with >300 lesions). This represents an 81% reduction in the expected number of varicella cases utilizing the historical attack rate of 87 % following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

In later clinical trials, a total of 1 114 children 1 to 12 years of age received 2 900 to 9 000 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 breakthrough varicella for up to 7 years post single-dose vaccination. This represents an approximate 94 % (95 % CI, 93 %, 96 %) compared with the age-adjusted expected incidence rates in susceptible subjects over the same period. In those who developed breakthrough varicella post-vaccination, the majority experienced mild disease with the median of the maximum total

number of lesions <50. The severity of reported breakthrough varicella, as measured by number of lesions and maximum temperature, appeared not to increase with time since vaccination.

Among a subset of vaccinees who were actively followed in these later trials for up to 7 years post-vaccination, 95 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella in 92 % (87/95) of exposed children, while 8 % (8/95) reported a mild form of varicella (maximum total number of lesions <50; observed range, 10 to 34). This represents an estimated efficacy of 90 % (95 % CI, 82 %, 96 %) based on the historical attack rate of 87 % following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

Among 9 202 children ≤12 years of age who received 1 injection of varicella vaccine (Oka/Merck), there were 1 149 cases of breakthrough varicella (occurring more than 6 weeks post-vaccination) 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.

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=1 114) or 2 doses of varicella vaccine (Oka/Merck) (n=1 102) 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 varicella zoster vaccine (VZV) antibody was measured annually for 9 years. Most cases of varicella reported in recipients of 1 dose or 2 doses of vaccine were mild. The estimated vaccine efficacy for the 10-year observation period was 94 % for 1 dose and 98 % for 2 doses ($p<0.001$). This translates to a 3.4-fold lower risk of developing varicella >42 days postvaccination during the 10-year observation period in children who received 2 doses than in those who received 1 dose

(2.2 % vs. 7.5 %, respectively).

There are 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).

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 to varicella, developed varicella.

The attack rate of unvaccinated adults exposed to a single contact in a household has not been previously studied. If the attack rate of 87 % following household exposure in susceptible children holds true for susceptible adolescents and adults, the estimated efficacy of the vaccine in the prevention of any varicella disease would range from 80 to 100 %.

There are 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).

Immunogenicity of Varicella Vaccine (Oka/Merck)

Clinical trials with several formulations of the vaccine containing attenuated virus ranging from 1 000 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 post-vaccination in 9 610 susceptible children 12 months to 12 years of age who received doses ranging from 1 000 to 50 000 PFU. Rates of breakthrough disease were significantly lower among children with varicella antibody titres ≥5 gpELISA units compared to children with titres <5 gpELISA units. Titres ≥5 gpELISA units were induced in approximately 83 % of children vaccinated with a single dose of vaccine at 1 000 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 titres ≥5 gpELISA units at 6 weeks post-vaccination, an approximate correlation 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 6 650 to 28 400 PFU per dose), was compared with that of the licensed frozen formulation (9 189 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 %.

Two-Dose Regimen in Children

In a multicenter study, 2216 healthy children 12 months to 12 years of age received either 1 dose of varicella vaccine (Oka/Merck) or 2 doses administered 3 months apart. The immunogenicity results are as follows:

Table 3

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

	Varicella Vaccine (Oka/Merck)	Varicella Vaccine (Oka/Merck)2-Dose Regimen (3 Months Apart) (N=1102)

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

N = Number of subjects vaccinated.

n = Number of subjects included in immunogenicity analysis.

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

Two-Dose Regimen in Adolescents and Adults

In a multicenter study involving susceptible adolescents and adults 13 years of age and older, 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 varicella are unknown.

Persistence of Immune Response

One-Dose Regimen in Children

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 % (3 092/3 120) at 1 year, 99.4 % (1 382/1 391) at 2 years, 98.7 % (1 032/1 046) at 3 years, 99.3 % (997/1 004) at 4 years, 99.2 % (727/733) at 5 years, and 100 % (432/432) at 6 years post-vaccination.

Two-Dose Regimen in Children

In recipients of 1 dose of varicella vaccine (Oka/Merck) 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 firstyear of follow-up and generally comparable thereafter. The cumulative rate of VZV antibody persistence with both regimens remained very high at year 9 (99.0 % for the 1-dose group and 98.8 % for the 2-dose group).

Two-Dose Regimen in Adolescents and Adults

In clinical studies involving healthy adolescents and adults who received 2 doses of vaccine, detectable 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 post-vaccination.

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 varicella are unknown.

Vaccination with ONVARA (Refrigerated) may not result in protection of all healthy, susceptiblechildren, adolescents, and adults.

Studies with other vaccines

Concomitant Administration with M-M-R II

In combined clinical studies involving 1 107 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 post-vaccination 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 (refer to section **4.5**).

Concomitant Administration with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Oral Poliovirus Vaccine (OPV)

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.

Concomitant Administration with PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

In a clinical study involving 306 children 12 to 18 months of age, 151 received an investigational varicella-containing 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 OMZYTA concomitantly with a booster dose of PedvaxHIB followed by ONVARA 6 weeks later. At six weeks post-vaccination, seroconversion rates for measles, mumps, rubella, and VZV, and GMTs for PedvaxHIB were comparable between the two groups. Anti-VZV levels were decreased when the investigational vaccine containing varicella was administered concomitantly with PedvaxHIB. No clinically significant differences in adverse reactions were seen between the two groups.

Concomitant Administration with OMZYTA and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine

In a clinical study involving 822 children 12 to 15 months of age, 410 received *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine, OMZYTA, and ONVARA concomitantly at separate injection sites, and 412 received *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine followed by OMZYTA and ONVARA given concomitantly at separate injection sites, 6 weeks later. At 6 weeks post-vaccination, the immune responses for the subjects who received the concomitant doses of *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combined vaccine, OMZYTA, and ONVARA were similar to those of the subjects who received COMVAX followed 6 weeks later by OMZYTA and ONVARA with respect to all antigens administered. There were no clinically important differences in reaction rates when the three vaccines were administered concomitantly versus six weeks apart.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Powder:

Anhydrous disodium phosphate

Hydrolysed gelatine

Monosodium L-glutamate

Potassium dihydrogen phosphate

Potassium chloride

Sodium chloride

Sucrose

Urea

Solvent:

Water for Injections

6.2 Incompatibilities

The vaccine must not be reconstituted with other medicinal products except those mentioned in section **6.6**.

6.3 Shelf-life

24 months

After reconstitution, the vaccine should be used immediately. However, the in-use stability has been demonstrated for 30 minutes between 20 ºC and 25 ºC.

Discard the vaccine if it is not used within 30 minutes after its preparation.

6.4 Special precautions for storage

Store in a refrigerator at 2 ºC to 8 ºC. Keep vial in the outer carton to protect from light.

Do not freeze.

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. **DO NOT STORE THE COMBINATION PACK IN THE FREEZER.**

Keep out of reach of children.

6.5 Nature and contents of container

Vial

3 ml clear Type 1 borosilicate glass vial with a grey rubber stopper and a silver aluminium cap with a blue plastic cap.

Sterile Diluent Vial

0,7 ml water for injection in a 3 ml glass vial with grey rubber stopper and dark grey plastic flip-off cap.

3 ml vial of ONVARA and 3 ml vial of DILUENT is packed together in a cardboard carton with the package insert and patient information leaflet.

Pack sizes of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of ONVARA 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. ONVARA when reconstituted is a clear, colourless to pale yellow liquid.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House

1685

South Africa

8. REGISTRATION NUMBER

48/30.2/1059

9. DATE OF FIRST AUTHORISATION

25 November 2016

10. DATE OF REVISION OF THE TEXT

06 August 2024