Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

VARIVAX powder and solvent for suspension for injection in a pre-filled syringeVaricella Vaccine (live)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:

Varicella virus* Oka/Merck strain (live, attenuated) ≥1350 PFU**
* Produced in human diploid cells (MRC-5)
** PFU = Plaque-forming units

This vaccine may contain a trace amount of neomycin (see sections 4.3 and 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

White to off-white powder and clear, colourless liquid solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VARIVAX is indicated for vaccination against varicella in individuals from 12 months of age (see sections 4.2 and 5.1).

VARIVAX can be administered to infants from 9 months of age under special circumstances, such as to conform with national vaccination schedules or in outbreak situations (see sections 4.2, 4.5, and 5.1).

VARIVAX may also be administered to susceptible individuals who have been exposed to varicella. Vaccination within 3 days of exposure may prevent a clinically apparent infection or modify the course of the infection. In addition, there are limited data that indicate that vaccination up to 5 days after exposure may modify the course of the infection (see section 5.1).

4.2 Posology and method of administration

Posology

The use of VARIVAX should be based on official recommendations.

Individuals less than 9 months of age
VARIVAX should not be administered to individuals less than 9 months of age.

Individuals from 9 months of age
Individuals should receive two doses of VARIVAX to ensure optimal protection against varicella (see section 5.1).

- Individuals from 9 to 12 months of age

In settings in which vaccination is initiated between 9 and 12 months of age, a second dose is needed and should be given after a minimum interval of 3 months (see section 5.1).

- Individuals from 12 months to 12 years of age

For individuals from 12 months to 12 years of age, at least one month must elapse between the first and second dose (see section 5.1).

Note: applicable official recommendations may vary regarding the need for one or two doses and the interval between doses of varicella-containing vaccines.

Individuals 12 months to 12 years of age with asymptomatic HIV infection [CDC Class 1] with an age-specific CD4+ T-lymphocyte percentage ≥25% should receive two doses given 12 weeks apart.

- Individuals from 13 years of age and older

Individuals from 13 years of age and older should receive two doses given 4-8 weeks apart. If the interval between doses exceeds 8 weeks, the second dose should be given as soon as possible (see section 5.1).

There are data available on protective efficacy for up to 9 years post-vaccination (see section 5.1). However, the need for booster doses has not been determined yet.

If VARIVAX is to be administered to seronegative subjects before a period of planned or possible future immunosuppression (such as those awaiting organ transplantation and those in remission from a malignant disease), the timing of the vaccinations should take into account the interval after the second dose before maximal protection might be expected (see sections 4.3, 4.4, and 5.1).

There are no data on protective efficacy or immune responses to VARIVAX in seronegative persons over 65 years of age.

Method of administration

The vaccine is to be injected intramuscularly (IM) or subcutaneously (SC).

The preferred injection sites are the anterolateral area of the thigh in younger children and the deltoid area in older children, adolescents, and adults.

The vaccine should be administered subcutaneously in patients with thrombocytopenia or any coagulation disorder.

DO NOT INJECT INTRAVASCULARLY.

Precautions to be taken before manipulating or administering the product:See section 6.6.

4.3 Contraindications

- Hypersensitivity to any varicella vaccine, to any of the excipients listed in section 6.1, or neomycin (which may be present as a trace residue, see sections 2 and 4.4).
- Blood dyscrasias, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the hemic and lymphatic systems.
- Individuals receiving immunosuppressive therapy (including high doses of corticosteroids) (see section 4.8).
- Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinaemia and AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25%; children between 12-35 months: CD4+ <20%; children between 36-59 months: CD4+ <15% (see sections 4.4 and 4.8).
- Individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.
- Active untreated tuberculosis.
- Any illness with fever >38.5ºC; however, low-grade fever itself is not a contraindication to vaccination.
- Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

As for other vaccines, there is the possibility of hypersensitivity reactions, not only to the active principle, but also to any of the excipients listed in section 6.1 or neomycin (which may be present as a trace residue, see sections 2 and 4.3).

As with other vaccines, VARIVAX does not completely protect all individuals from naturally acquired varicella. Clinical trials have only assessed efficacy beginning 6 weeks after a single dose in healthy individuals up to 12 years of age or 6 weeks after the second dose in older subjects (see section 5.1).

Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (e.g., asymptomatic HIV subjects, IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases).

Immunocompromised patients who have no contraindication for this vaccination (see section 4.3) may not respond as well as immunocompetent subjects; therefore, some of these patients may acquire varicella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of varicella.

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination (see section 4.5).

Transmission
Transmission of varicella vaccine virus (Oka/Merck strain) resulting in varicella infection including disseminated disease may rarely occur between vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella including healthy as well as high-risk individuals(see section 4.8).

Therefore, vaccine recipients should attempt to avoid, whenever possible, close association with susceptible high-risk individuals for up to 6 weeks following vaccination.

In circumstances where contact with high-risk individuals is unavoidable, before vaccination, the potential risk of transmission of the vaccine virus should be weighed against the risk of acquiring and transmitting the wild-type varicella virus (see section 4.8).

Susceptible high-risk individuals include:

- Immunocompromised individuals (see section 4.3);
- Pregnant women without documented positive history of chickenpox or laboratory evidence of prior infection;
- New-borns of mothers without documented positive history of chickenpox or laboratory evidence of prior infection.

Sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per dose and is considered to be essentially 'sodium-free'.

Potassium
This medicinal product contains less than 1 mmol (39 mg) potassium per dose and is considered to be essentially 'potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

VARIVAX must not be mixed with any other vaccine or other medicinal product in the same syringe. Other injectable vaccines or other medicinal products must be given as separate injections and at different body sites.

Concomitant administration with other vaccines
VARIVAX 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 vaccine, hepatitis B 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 VARIVAX. 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 VARIVAX and tetravalent, pentavalent or hexavalent (diphtheria, tetanus, and acellular pertussis [DTaP])-based vaccines has not been evaluated.

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

Administration of varicella zoster virus antibody-containing blood products, including VZIG or other immune globulin preparations, within 1 month following a dose of VARIVAX may reduce the immune response to the vaccine and hence reduce its protective efficacy. Therefore, administration of any of these products should be avoided within 1 month after a dose of VARIVAX unless considered to be essential.

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX as Reye syndrome has been reported following use of salicylates during wild-type varicella infection *(see section 4.4)*.

4.6 Fertility, pregnancy and lactation

Fertility
Animal reproduction studies have not been conducted with VARIVAX. VARIVAX has not been evaluated for potential to impair fertility.

Pregnancy
Pregnant women should not be vaccinated with VARIVAX.

Studies have not been conducted with VARIVAX in pregnant women.
However, foetal damage has not been documented when varicella vaccines have been given to pregnant women. It is not known whether VARIVAX can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity.

Pregnancy should be avoided for 1 month following vaccination. Women who intend to become pregnant should be advised to delay.

Breast-feeding
Due to the theoretical risk of transmission of the vaccine viral strain from mother to infant, VARIVAX is not generally recommended for breast-feeding mothers (see also section 4.4). Vaccination of exposed women with negative history of varicella or known to be seronegative to varicella should be assessed on an individual basis.

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

a. Summary of the safety profile

In clinical trials, frozen and refrigerator-stable formulations of varicella vaccine (live) (Oka/Merck strain) were administered to approximately 17,000 healthy individuals ≥12 months of age who were monitored for up to 42 days after each dose. There appeared to be no increased risk for adverse events with the use of VARIVAX in seropositive individuals. The safety profile of refrigerator-stable varicella vaccine (live) (Oka/Merck strain) was generally similar to the safety profile for earlier formulations of the vaccine.

In a double-blind, placebo-controlled study among 956 healthy individuals 12 months to 14 years of age, 914 of whom were serologically confirmed to be susceptible to varicella, the only adverse events that occurred at a significantly greater rate in vaccine recipients than in placebo recipients were pain (26.7% versus 18.1%) and redness (5.7% versus 2.4%) at the injection site and non-injection-site varicella-like rash (2.2% versus 0.2%).

In a clinical trial, 752 children received VARIVAX, either intramuscularly or subcutaneously. The general safety profile of either administration routes were comparable, although injection-site reactions were less frequent in the IM group (20.9%) compared with the SC group (34.3%).

In a post-marketing study with varicella vaccine (live) (Oka/Merck strain), 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 3600 individuals, 13 years of age and older, no vaccine-related serious adverse events were reported.

b. Tabulated summary of adverse reactions

Clinical studies

Across clinical studies in which causality was assessed (5185 subjects), the following adverse events were reported in temporal association with vaccination:

Adverse events are ranked under headings of frequency using the following convention:

Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000)

Healthy individuals 12 months to 12 years of age (1 dose)

Adverse events	**Frequency**
Blood and the lymphatic system disorders	
Lymphadenopathy, Lymphadenitis, Thrombocytopenia	Rare
Nervous system disorders	
Headache, Somnolence	Uncommon
Apathy, Agitation, Hypersomnia, Gait abnormality, Febrile seizure, Tremor	Rare
Eye disorders	
Conjunctivitis	Uncommon
Acute conjunctivitis, Tearing, Oedema of the eyelid, Irritation	Rare
Ear and labyrinth disorders	
Ear pain	Rare
Respiratory, thoracic and mediastinal disorders	
Cough, Nasal congestion, Respiratory congestion, Rhinorrhoea	Uncommon
Sinusitis, Sneezing, Pulmonary congestion, Rhinitis, Wheezing, Bronchitis, Respiratory infection, Pneumonia	Rare
Metabolism and nutrition disorders	
Anorexia	Uncommon
Infections and infestations	
Upper respiratory infection	Common
Gastroenteritis, Otitis, Otitis media, Pharyngitis, Varicella, Viral exanthema, Viral infection	Uncommon
Infection, Flu-like illness	Rare
Gastrointestinal disorders	
Diarrhoea, Vomiting	Uncommon
Abdominal pain, Nausea, Haematochezia, Mouth ulcer	Rare
Skin and subcutaneous tissue disorders	
Rash, Maculopapular rash, Varicella-like rash (generalised median 5 lesions)	Common
Contact dermatitis, Erythema, Pruritus, Urticaria	Uncommon
Flushing, Vesicle, Atopic dermatitis, Hive-like rash, Contusion, Dermatitis, Drug eruption, Skin infection	Rare
Musculoskeletal and connective site conditions	
Musculoskeletal pain, Myalgia, Stiffness	Rare
Vascular disorders	
Extravasation	Rare
General disorders and administration site conditions	
Fever	Very common
Injection site erythema, Rash, Pain/Tenderness/Soreness, Swelling, and Varicella-like rash (injection site median 2 lesions)	Common

Asthenia/Fatigue, Injection site ecchymosis, Haematoma, Induration, Rash, Malaise	Uncommon
Injection site eczema, Lump, Warmth, Hive-like rash, Discolouration, Inflammation, Stiffness, Oedema/Swelling, Warm sensation, Warm to touch	Rare
Psychiatric disorders	
Irritability	Common
Crying, Insomnia, Sleep disorder	Uncommon

Healthy individuals 12 months to 12 years of age (2 doses received ≥ 3 months apart)

The following serious adverse events temporally associated with the vaccination were reported in individuals 12 months to 12 years of age given varicella vaccine (live) (Oka/Merck strain): diarrhoea, febrile seizure, fever, post-infectious arthritis, vomiting.

The rates of systemic clinical adverse events after a second dose of VARIVAX were generally similar to, or lower than, those seen with the first dose. The rates of injection-site reactions (primarily erythema and swelling) were higher after a second dose (see section 5.1 for study description).

Healthy individuals 13 years of age and older (majority received 2 doses 4 to 8 weeks apart)

Causality was not assessed in individuals 13 years of age and older with the exception of serious adverse events. However, across clinical studies (1648 subjects) the following events were temporally associated with vaccination:

Adverse events	**Frequency**
Skin and subcutaneous tissue disorders	
Varicella-like rash (generalised median 5 lesions)	Common
General disorders and administration site conditions	
Fever ≥37.7°C oral, Injection-site erythema, Soreness and Swelling	Very common
Injection-site rash, Pruritus and Varicella-like rash (injection site median 2 lesions)	Common
Injection-site ecchymosis, Haematoma, Induration, Numbness and Warmth	Uncommon
Hyperpigmentation, Stiffness	Rare

Post-Marketing Surveillance

The following adverse events have been spontaneously reported in temporal relation to VARIVAX during worldwide post-marketing use:

Adverse events[+]
Blood and the lymphatic system disorders
Aplastic anaemia, Thrombocytopenia (including idiopathic thrombocytopenic purpura (ITP)), Lymphadenopathy
Nervous system disorders
Cerebrovascular accident, Febrile and non-febrile convulsions, Guillain-Barré syndrome, Transverse myelitis, Bell's palsy, Ataxia*, Vertigo/Dizziness, Paraesthesia, Syncope
Respiratory, thoracic and mediastinal disorders
Pneumonitis
Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome, Erythema multiforme, Henoch-Schönlein purpura, Secondary bacterial infections of skin and soft tissues, including Cellulitis
Infections and infestations
Encephalitis*[‡], Pharyngitis, Pneumonia*, Varicella (vaccine strain), Herpes zoster*[‡], Aseptic meningitis[‡]
General disorders and administration site conditions
Irritability
Immune system disorders
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
Gastrointestinal disorders
Nausea, Vomiting

[+] Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequency of these adverse events is qualified as "not known".
* These selected adverse events reported with varicella vaccine (live) (Oka/Merck strain) are also a consequence of wild-type varicella infection. There is no indication of an increased risk of these adverse events following vaccination compared with wild-type disease from active post-marketing surveillance studies or passive post-marketing surveillance reporting (see section 5.1).
[‡] See section c.

Postvaccination rashes in which the Oka/Merck strain was isolated were generally mild (see section 5.1).

c. Description of selected adverse reactions

Cases of herpes zoster in clinical studies
In clinical trials, 12 cases of herpes zoster have been reported in 9543 vaccinated individuals 12 months to 12 years of age during 84,414 person-years of follow-up. This resulted in a calculated incidence of at least 14 cases per 100,000 person-years, compared with 77 cases per 100,000 person-years following wild-type varicella infection. In 1652 vaccinated individuals 13 years of age and older, 2 cases of herpes zoster were reported. All 14 cases were mild and no sequelae were reported.

In another clinical study in individuals 12 months to 12 years of age, there were 2 cases of herpes zoster reported in the group receiving one dose of the vaccine and no cases were reported in the two-dose group. The subjects were followed for 10 years postvaccination.

Active surveillance data in children vaccinated with varicella vaccine (live) (Oka/Merck strain) and followed for 14 years after vaccination showed no increase in the frequency of herpes zoster compared to children with prior wild-type varicella during the pre-vaccine era. However, the long-term effect of varicella vaccine (live) (Oka/Merck strain) on the incidence of herpes zoster is unknown at present (see section 5.1).

Complications associated with varicella
Complications of varicella from vaccine strain, including herpes zoster and disseminated disease such as aseptic meningitis and encephalitis, have been reported in immunocompromised and immunocompetent individuals.

Transmission
Based on isolated case reports from post-marketing surveillance, the vaccine virus may rarely be transmitted to contacts of vaccinees who develop or do not develop a varicella-like rash (see section 4.4).

Concomitant use of varicella vaccine (live) (Oka/Merck strain) with other paediatric vaccines
When varicella vaccine (live) (Oka/Merck strain) was given concurrently with measles, mumps, rubella vaccine (M-M-R II) to 12- to 23-month-old individuals, fever (≥38.9°C; oral equivalent, Days 0 to 42 postvaccination) was reported at a rate of 26-40% (see also section 4.5).

d. Other special population

Immunocompromised individuals (see section 4.3)
Necrotising retinitis has been reported post-marketing in immunocompromised individuals.

Elderly
Clinical trial experience has not identified differences in the safety profile between the elderly (individuals ≥65 years of age) and younger subjects.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Accidental administration of more than the recommended dose of varicella vaccine (live) (Oka/Merck strain) has been reported (either a larger dose than recommended was injected, more than one injection was given, or the interval between injections was shorter than that recommended). Of these cases, the following adverse events were reported: injection-site redness, soreness, inflammation; irritability; gastrointestinal complaints (i.e., haematemesis, faecal emesis, gastroenteritis with vomiting and diarrhoea); cough and viral infection. None of the cases had long-term sequelae.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: virus vaccines - varicella viruses

ATC code: J07BK01

Evaluation of clinical efficacy

Efficacy in individuals less than 12 months of age
Clinical efficacy has not been evaluated when vaccination was initiated at less than 12 months of age.

One-dose regimen in healthy individuals 12 months to 12 years of age
In combined clinical trials using earlier formulations of the varicella vaccine (live) (Oka/Merck strain) at doses ranging from approximately 1000 to 17,000 PFU, the majority of subjects who received the varicella vaccine (live) (Oka/Merck strain) and were exposed to wild-type virus were either completely protected from chickenpox or developed a milder form of the disease. In particular, the protective efficacy of varicella vaccine (live) (Oka/Merck strain) beginning 42 days postvaccination was evaluated in three different ways:

1) by a double-blind, placebo-controlled trial over 2 years (N=956; efficacy 95 to 100%; formulation containing 17,430 PFU);

2) by assessment of protection from disease following household exposure over 7 to 9 years of observation (N=259; efficacy 81 to 88%; formulation containing 1000-9000 PFU); and

3) by comparing chickenpox rates over 7 to 9 years in vaccinees versus historical control data from 1972 through 1978 (N=5404; efficacy 83 to 94%; formulation containing 1000-9000 PFU).

In a group of 9202 individuals 12 months to 12 years of age who had received a dose of the varicella vaccine (live) (Oka/Merck strain), 1149 cases of infection (occurring more than 6 weeks postvaccination) were observed over a follow-up period of up to 13 years. Out of these 1149 cases, 20 (1.7%) were classified as severe (number of lesions ≥300, oral body temperature ≥37.8°C). The above-mentioned data, compared with the 36% proportion of severe cases observed following the wild-type virus infection in the unvaccinated historical controls, corresponds to a 95% relative decrease in the proportion of severe cases observed in the vaccinees who acquired infection after vaccination.

Prophylaxis of varicella by vaccination up to 3 days following exposure has been investigated in two small controlled trials. The first study demonstrated that none of 17 children developed varicella following household exposure compared with 19 of 19 unvaccinated contacts. In a second placebo-controlled trial of post-exposure prophylaxis, one of 10 children in the vaccine group versus 12 of 13 in the placebo group developed varicella. In an uncontrolled trial in a hospital setting, 148 patients, of whom 35 were immunocompromised, received a dose of varicella vaccine 1 to 3 days post-exposure and none developed varicella.

Published data on prevention of varicella at 4 to 5 days post-exposure are limited. In a double-blind trial, 26 susceptible siblings of children with active varicella were randomised to placebo or varicella vaccine. In the varicella vaccine group, 4 of 13 children (30.8%) developed varicella, of whom 3 children were vaccinated on Days 4 to 5. However, the disease was mild (1, 2, and 50 lesions). In contrast, 12 of 13 children (92.3%) in the placebo group developed typical varicella (60 to 600 lesions). Thus, vaccination 4 to 5 days after exposure to varicella may modify the course of any secondary cases of varicella.

Two-dose regimen in healthy individuals 12 months to 12 years of age

In a study comparing 1-dose (N=1114) and 2-doses (N=1102) given 3 months apart, the estimated efficacy against all severities of varicella disease for the 10-year observation period was 94% for 1-dose and 98% for 2 doses (p<0.001). The cumulative rate of varicella over the 10-year observation period was 7.5% after 1 dose and 2.2% after 2 doses. Most cases of varicella reported in recipients of 1 dose or 2 doses were mild.

Two-dose regimen in healthy individuals 13 years of age and older
Protective efficacy following two doses given 4 or 8 weeks apart in individuals 13 years of age or older was evaluated based on household exposure over 6 to 7 years after vaccination. The clinical efficacy rate ranged from approximately 80 to 100%.

Immunogenicity of varicella vaccine (live) (Oka/Merck strain)
One-dose regimen in individuals 12 months to 12 years of age
Clinical studies have established that the immunogenicity of the refrigerator-stable formulation is similar to the immunogenicity of earlier formulations that were evaluated for efficacy.

A titre ≥5 gpELISA units/mL (gpELISA is a highly sensitive assay that is not commercially available) at 6 weeks postvaccination has been shown to be an approximate correlate of clinical protection. However, it is not known whether a titre of ≥0.6 gpELISA units/mL correlates with long-term protection.

Humoral immune response in individuals 12 months to 12 years of age
Seroconversion (based on assay cut-off that generally corresponds to ≥0.6 gpELISA units/mL) was observed in 98% of 9610 susceptible individuals 12 months to 12 years of age who received doses ranging from 1000 to 50,000 PFU. Varicella antibody titres ≥5 gpELISA units/mL were induced in approximately 83% of these individuals.

In individuals 12 to 23 months of age, the administration of VARIVAX refrigerated (8000 PFU/dose or 25,000 PFU/dose) induced varicella antibody titres ≥5 gpELISA units/mL at 6 weeks postvaccination, in 93% of individuals vaccinated.

Humoral immune response in individuals 13 years of age and older
In 934 individuals 13 years of age and older, several clinical trials with varicella vaccine (live) (Oka/Merck strain) at doses ranging from approximately 900 to 17,000 PFU, have shown a seroconversion rate (varicella antibody titre ≥0.6 gpELISA units/mL) after 1 dose of vaccine ranging from 73 to 100%. The proportion of subjects with antibody titres ≥5 gpELISA units/mL ranged from 22 to 80%.

After 2 doses of vaccine (601 subjects) at doses ranging from approximately 900 to 9000 PFU, the seroconversion rate ranged from 97 to 100% and the proportion of subjects with antibody titres ≥5 gpELISA units/mL ranged from 76 to 98%.

There are no data on immune responses to VARIVAX in Varicella-zoster virus (VZV)-seronegative persons ≥65 years of age.

Humoral immunity according to route of administration
A comparative study in 752 subjects who received VARIVAX either by intramuscular route or subcutaneous route demonstrated a similar immunogenicity profile with both administration routes.

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

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

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

given 3 to 6 years apart are comparable to those obtained when the 2 doses are given 3 months apart. The seroconversion rates were approximately 100% after the first dose and 100% after the second dose. The vaccine seroprotection rates (≥5 gpELISA units/mL) were approximately 85% after the first and 100% after the second dose and the geometric mean titre (GMT) rose an average of approximately 10-fold after the second dose (for safety see section 4.8).

Two-dose regimen in healthy individuals 9 to 12 months of age at the time of first dose

A clinical study was conducted with the combined measles, mumps, rubella and varicella (Oka/Merck) (MMRV) vaccine administered with a 2-dose schedule, the doses being given 3 months apart in 1,620 healthy subjects from 9 to 12 months of age at the time of first dose.

The safety profile post-dose 1 and 2 was generally comparable for all age cohorts.

In the Full Analysis Set (vaccinated subjects regardless of their antibody titre at baseline), seroprotection rates of 100% were elicited to varicella post-dose 2, regardless of the age of the vaccinee at the first dose.

The seroprotection rates and geometric mean titres (GMTs) to varicella for the Full Analysis Set are provided in the following table.

	MMRV Vaccine Dose 1 at 9 months / Dose 2 at 12 months (N = 527)		MMRV Vaccine Dose 1 at 11 months / Dose 2 at 14 months (N = 480)		MMRV Vaccine Dose 1 at 12 months / Dose 2 at 15 months (N = 466)	
	6 Weeks Post-dose 1	6 Weeks Post-dose 2	6 Weeks Post-dose 1	6 Weeks Post-dose 2	6 Weeks Post-dose 1	6 Weeks Post-dose 2
Seroprotection rateto varicella [95% CI] (titre ≥5 gpELISA units/mL)	93.1% [90.6; 95.1]	100% [99.3; 100]	97.0% [95.1; 98.4]	100% [99.2; 100]	96.5% [94.4; 98.0]	100% [99.2; 100]
Geometric mean titres [95% CI] (gpELISA units/mL)	12 [12; 13]	321 [293; 352]	15 [14; 15]	411 [376; 450]	15 [14; 15]	481 [441; 526]

Duration of immune response
One-dose regimen in individuals 12 months to 12 years of age
In those clinical studies involving healthy individuals 12 months to 12 years of age who have been followed long-term after single-dose vaccination, detectable varicella antibodies (gpELISA ≥0.6 units/ mL) 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 individuals 12 months to 12 years of age
Over 9 years of follow-up, the GMTs and percent of subjects with VZV antibody titres ≥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 comparable during the entire follow-up period. 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).

Individuals 13 years of age and older
In clinical studies involving healthy individuals 13 years of age and older who received 2 doses of vaccine, detectable varicella antibodies (gpELISA ≥0.6 units/mL) 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 immune response following administration ofvaricella vaccine (live) (Oka/Merck strain) in the absence of wild-type boosting is unknown (see section 4.2).

Immune memory was demonstrated by administering a booster dose of varicella vaccine (live) (Oka/Merck strain) 4 to 6 years after the first vaccination in 419 individuals who were 1 to 17 years of age at the time of the first injection. The GMT prior to the booster dose was 25.7 gpELISA units/mL and increased to 143.6 gpELISA units/mL approximately 7-10 days after the booster dose.

Effectiveness of varicella vaccine (live) (Oka/Merck strain)

Observational studies of long-term effectiveness of VARIVAX
Surveillance data from two U.S. observational effectiveness studies confirmed that widespread varicella vaccination reduces the risk of varicella by approximately 90%. Furthermore, the reduced risk of varicella was maintained at the population level over at least 15 years both in vaccinated and unvaccinated individuals. The data also suggest that varicella vaccination may reduce the risk of herpes zoster in vaccinated individuals.

In the first study, a long-term prospective cohort study, approximately 7,600 children vaccinated in 1995 with varicella vaccine in their second year of life were actively followed for 14 years in order to estimate the occurrence of varicella and herpes zoster. By the end of the study in 2009, 38% of the study children were known to have received a second dose of varicella vaccine. Of note, in 2006, a second dose of varicella vaccine was recommended in the U.S. Over the entire follow-up, the incidence of varicella was approximately 10-fold lower among vaccinees than among children of the same age in the pre-vaccine era (estimated vaccine effectiveness over the study period was between 73% and 90%). Regarding herpes zoster, there were fewer herpes zoster cases among varicella vaccinees during the follow-up period than expected from rates in children of the same age with prior wild-type varicella during the pre-vaccine era (relative risk = 0.61, 95% CI 0.43 - 0.89). Breakthrough varicella and zoster cases were usually mild.

In a second long-term surveillance study, five cross-sectional surveys on varicella incidence, each from a random sample of approximately 8,000 children and adolescents 5 to 19 years of age, were conducted over 15 years, from 1995 (pre-vaccine) through 2009. Results showed a gradual decline of varicella rates by an overall 90% to 95% (approximately 10- to 20-fold) from 1995 to 2009 in all age groups, both in vaccinated and unvaccinated children and adolescents. In addition, a decrease by approximately 90% (approximately 10-fold) in varicella hospitalisation rates was observed in all age groups.

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

For information regarding residual components in trace quantities, see sections 2, 4.3 and 4.4.

Solvent:
Water for Injections

6.2 Incompatibilities

The vaccine must not be mixed with other medicinal products.

6.3 Shelf life

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

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C). Keep vial in the outer carton to protect from light.

Do not freeze.

For storage conditions after the reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial
Powder in a 3 mL vial (Type I glass) with stopper (butyl rubber) and flip-off cap (aluminium).

Pre-filled syringe
Solvent in a 1 mL pre-filled syringe (Type I glass) with plunger stopper (chlorobutyl rubber) and tip cap (styrene-butadiene rubber), without needle.
Solvent in a 1 mL pre-filled syringe (Type I glass) with plunger stopper (chlorobutyl rubber) and tip cap (styrene-butadiene rubber), with 2 separate needles in the blister.

Pack of one and ten doses.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before reconstitution, the vial contains a white to off-white powder and the pre-filled syringe contains a clear, colourless liquid solvent. The reconstituted vaccine is a clear, colourless to pale yellow liquid.

Avoid contact with disinfectants.

To reconstitute the vaccine, use only the solvent provided in the pre-filled syringe.

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.

One needle should be used for reconstitution and a separate, new needle for injection.

Directions for the vaccine preparation

To attach the needle, it should be firmly placed on the tip of the syringe and secured by rotating a quarter of a turn (90°).

Inject the entire content of the pre-filled syringe into the vial containing the powder. Gently agitate to mix thoroughly.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation in physical appearance. The vaccine must not be used if any particulate matter is noted or if the appearance is not a clear colourless to pale yellow liquid after reconstitution.

It is recommended that the vaccine be administered immediately after reconstitution, to minimise loss of potency. Discard if reconstituted vaccine is not used within 30 minutes.

Do not freeze the reconstituted vaccine.

Withdraw the entire content of the vial into a syringe, change the needle, and inject the vaccine by subcutaneous or intramuscular route.

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

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ireland (Human Health) Limited
Red Oak North
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

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Date of last renewal: 19 December 2006

10 DATE OF REVISION OF THE TEXT

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