# Product Information as approved by the CHMP on 13 December 2012, pending endorsement by the European Commission

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection.
Measles, mumps, rubella and varicella vaccine (live).

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 ml) contains:

Measles virus[1] Enders' Edmonston strain (live, attenuated)..... not less than 3.00 $log_{10}$ $CCID_{50}$*
Mumps virus[1] Jeryl Lynn™ (Level B) strain (live, attenuated)... not less than 4.30 log10 $CCID_{50}$*
Rubella virus[2] Wistar RA 27/3 strain (live, attenuated)..... not less than 3.00 log10 $CCID_{50}$*
Varicella virus[3] Oka/Merck strain (live, attenuated) ..... not less than 3.99 log10 PFU**

*50% cell culture infectious dose
**plaque-forming units

([1]) Produced in chick embryo cells.
([2]) Produced in human diploid lung (WI-38) fibroblasts.
([3]) Produced in human diploid (MRC-5) cells.

This vaccine contains a trace amount of neomycin. See section 4.3.

Excipients with known effect:
Sorbitol 16 mg
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Before reconstitution, the powder is a white to pale yellow compact crystalline cake and the solvent is a clear colourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ProQuad is indicated for simultaneous vaccination against measles, mumps, rubella and varicella in individuals from 12 months of age.

ProQuad can be administered to individuals from 9 months of age under special circumstances (e.g., to conform with national vaccination schedules, outbreak situations, or travel to a region with high prevalence of measles; see sections 4.2, 4.4, and 5.1).

### 4.2 Posology and method of administration

Posology

ProQuad should be used in accordance to official recommendations.

- Individuals 12 months of age and older

Individuals from 12 months of age should receive two doses of ProQuad or a single dose of ProQuad followed by a second dose of a monovalent varicella vaccine to ensure optimal protection against varicella (see section 5.1). At least one month must elapse between the first and second dose of any live viral attenuated vaccine. It is preferred that the second dose be administered within three months following the first dose.

- Individuals between 9 and 12 months of age
  Immunogenicity and safety data show that ProQuad can be administered to individuals between 9 and 12 months of age, under special circumstances (e.g., in accordance with official recommendations or when early protection is considered necessary). In such cases, individuals should receive a second dose of ProQuad, given a minimum of 3 months apart, to ensure optimal protection against measles and varicella (see sections 4.4 and 5.1).

- Individuals less than 9 months of age
  ProQuad is not indicated in this subset of the paediatric population. The safety and efficacy of ProQuad in children under 9 months of age have not been established.

ProQuad may be used as the second dose in individuals who have previously received measles, mumps, and rubella vaccine and varicella vaccine.

Method of administration
The vaccine is to be injected by the subcutaneous route in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

**DO NOT INJECT INTRAVASCULARLY.**

## 4.3 Contraindications

History of hypersensitivity to any varicella vaccine or measles, mumps, or rubella vaccine, to any of the excipients, or to neomycin, which may be present as trace residues (see sections 2, 4.4 and 6.1).

Blood dyscrasias, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the haematopoietic and lymphatic system.

Current immunosuppressive therapy (including high doses of corticosteroids). ProQuad is not contraindicated in individuals who are receiving topical or low-dose parenteral corticosteroids (e.g. for asthma prophylaxis or replacement therapy).

Severe humoral or cellular (primary or acquired) immunodeficiency, e.g., severe combined immunodeficiency, agammaglobulinemia 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 section 4.4).

In severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine, measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported.

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

Active untreated tuberculosis. Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine. No studies have been reported to date on the effect of measles virus vaccines on children with untreated tuberculosis.

Vaccination should be postponed during any illness with fever >38.5°C.

Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

## 4.4 Special warnings and precautions for use

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Additionally, live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g. hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination in such cases.

Due caution should be employed in the administration of ProQuad to persons with individual or family history of convulsions, or a history of cerebral injury. The physician should be alert to the temperature elevation that may occur following vaccination (see section 4.8).

Individuals less than 12 months of age who are vaccinated with a measles-containing vaccine during measles outbreaks or for other reasons may fail to respond to the vaccine due to the presence of circulating antibodies of maternal origin and/or immaturity of the immune system (see sections 4.2 and 5.1).

This vaccine contains 16 mg of sorbitol as an excipient. Patients with rare hereditary problems of fructose intolerance should not take this vaccine.

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

Vaccination with ProQuad may not result in protection in all vaccine recipients.

Transmission

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk; however, transmission of the rubella vaccine virus to infants via breast milk has been documented without any evidence of clinical disease (see section 4.6).

There are no reports of transmission of the more attenuated Enders' Edmonston strain of measles virus or the Jeryl Lynn™ strain of mumps virus from vaccine recipients to susceptible contacts.

Post-licensing experience with Varicella Vaccine live (Oka/Merck) suggests that transmission of varicella vaccine virus may rarely occur between healthy vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella, as well as high-risk individuals susceptible to varicella (see section 4.8).

High-risk individuals susceptible to varicella include:

- immunocompromised individuals (see section 4.3),
- pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection,
- newborn infants of mothers without documented positive history of varicella or laboratory evidence of prior infection.

Vaccine recipients should attempt to avoid, whenever possible, close association with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination. In circumstances where contact with high-risk individuals susceptible to varicella is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus.

Thrombocytopenia
In clinical trials, no cases were reported regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad. Cases of thrombocytopenia have been reported in post-marketing experience after primary vaccination with ProQuad. In addition, cases of thrombocytopenia have been reported after primary vaccination or revaccination with measles vaccine; measles, mumps, and rubella vaccine; and varicella vaccine. Post-marketing experience with live measles, mumps, and rubella vaccine indicates that individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia following the first dose of a live measles, mumps, and rubella vaccine may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The risk-to-benefit ratio should be carefully evaluated before considering vaccination with ProQuad in such cases (see section 4.8).

Febrile seizures
In the 5- to 12-day timeframe after the administration of the first dose of quadrivalent measles, mumps, rubella and varicella vaccines in children, an increased risk of febrile seizure was observed compared to concomitant administration of measles, mumps, rubella and varicella vaccines (see sections 4.8 and 5.1).

Other
Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (asymptomatic HIV patients, 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 patients; therefore, some of these patients may acquire measles, mumps, rubella, or varicella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of measles, parotitis, rubella, and varicella.

Post-exposure prophylaxis
No clinical data are available for ProQuad administered after exposure to measles, mumps, rubella, or varicella. However, post-exposure prophylaxis for varicella and measles has been demonstrated with Varicella Vaccine live (Oka/Merck) and the measles-containing vaccines manufactured by Merck & Co., Inc., respectively.

Interference with laboratory tests: see section 4.5.

## 4.5 Interaction with other medicinal products and other forms of interaction

At least 1 month should elapse between receipt of a live virus vaccine and ProQuad.

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad (see section 4.4).

Do not give immunoglobulin (IG) or Varicella Zoster Immune Globulin (VZIG) concomitantly with ProQuad.

Administration of immune globulins concomitantly with ProQuad may interfere with the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of immune globulins (IG). However, the appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (e.g. 5 months for VZIG).

Administration of varicella zoster virus antibody-containing blood products, including VZIG or other immune globulin preparations, within 1 month following a dose of ProQuad 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 ProQuad unless considered to be essential.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either any time before, simultaneously with, or at least 4 to 6 weeks after immunization with ProQuad.

Concomitant use with other vaccines:
Clinical studies have demonstrated that ProQuad can be given simultaneously (but at separate injection sites) with Prevenar and/or hepatitis A vaccine, or with monovalent or combination vaccines comprised of diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, or hepatitis B antigen. In these clinical studies, it was demonstrated that the immune responses were unaffected. The safety profiles of the administered vaccines were comparable (see section 4.8).

There are insufficient data to support the use of ProQuad with any other vaccines.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnant women should not be vaccinated with ProQuad.

Studies have not been conducted with ProQuad in pregnant women. It is not known whether ProQuad can cause foetal harm when administered to a pregnant woman or 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
Studies have shown that breast-feeding postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection, none had symptomatic disease. There is no evidence that varicella vaccine virus is excreted in breast milk. It is not known whether measles or mumps vaccine virus is secreted in human milk. Therefore, caution should be exercised when considering whether to administer ProQuad to a breast-feeding woman.

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

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machinery have been performed. ProQuad is expected to have no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

a. Summary of the safety profile

In 5 clinical trials, ProQuad was administered without concomitant vaccines to 6038 children 12 through 23 months of age. The children in these studies received either the current refrigerator-stable formulation or an earlier formulation of ProQuad. Children in these studies were monitored for six weeks post vaccination. The safety profiles were comparable for the two different formulations after a single dose. The only vaccine-related systemic adverse reactions reported at a significantly greater rate in individuals who received the earlier formulation of ProQuad compared to individuals who received the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. and Varicella Vaccine live (Oka/Merck) were fever (≥39.4°C rectal equivalent or abnormal) and measles-like rash. Both fever and measles-like rash usually occurred within 5 to 12 days following the vaccination, were of short duration and resolved with no long-term sequelae. Pain/tenderness/soreness at the injection site was reported at a statistically lower rate in individuals who received ProQuad.

The only vaccine related injection-site adverse reaction that was more frequent among recipients of ProQuad than among recipients of Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co. Inc. was rash at the injection site.

Following ProQuad given alone in 7 clinical trials, the observed rates of fever (≥39.4°C rectal equivalent) ranged from 10.1% to 39.4%. In comparison, following ProQuad given concomitantly with Prevenar and/or hepatitis A vaccine in 3 clinical trials, the observed rates of reported fever (≥39.4°C rectal equivalent) ranged from 15.2% to 27.2%.

In a clinical trial of ProQuad administered concomitantly with Infanrix Hexa, the rates of fever (≥38.0°C rectal equivalent) were 69.3% following concomitant administration, 61.1% following ProQuad alone, and 57.3% following Infanrix Hexa alone; the rates of fever (≥39.4°C rectal equivalent) were 22.6% following concomitant administration, 20.5% following ProQuad alone, and 15.9% following Infanrix Hexa alone.

The overall safety profile of ProQuad was comparable whether it was administered concomitantly or alone.

Children who received a second dose of ProQuad

In eight clinical studies, the overall rates of adverse reactions after a second dose of ProQuad were generally similar to, or lower than, those seen with the first dose. In three of these studies, the rates of injection-site erythema and swelling were statistically significantly higher after the second dose than after the first dose; however, in the remaining five studies, the rates of each of these reactions were similar after the first and second dose. The fever rate in all eight studies was lower after the second dose than after the first dose.

Children who received ProQuad at 4 through 6 years of age after primary immunization with Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.

The rates and types of adverse reactions seen in the study group that received ProQuad were generally similar to those seen in the groups that received Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. (see section 5.1 for study description).

No specific studies have been conducted in individuals from 2 years of age who had not previously received measles, mumps, rubella, and varicella vaccines.

The most common adverse events reported with the use of ProQuad were: injection-site reactions including pain/tenderness/soreness, redness, swelling or bruising; fever (≥39.4°C rectal equivalent); irritability; rash (including measles-like rash, varicella-like rash, and injection-site rash); upper respiratory infection; vomiting and diarrhoea.

b. Tabulated summary of adverse reactions

The following adverse reactions were reported as vaccine related by the investigator in individuals after a single dose of ProQuad. Several adverse events were solicited in the clinical studies and are designated with the symbol (‡). Additionally, other adverse experiences have been reported with post-marketing use of ProQuad and/or in clinical studies and post-marketing use of either the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., the monovalent component vaccines of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., or Varicella Vaccine live (Oka/Merck). These adverse effects are listed below without regard to causality or frequency (frequency *not known*).

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000), including isolated reports; not known (cannot be estimated from the available data)

| Adverse reactions | Frequency |
|---|---|
| **Infections and infestations** | |
| Upper respiratory infection | Common |
| Ear infection, Gastroenteritis, Nasopharyngitis, Otitis media, Pharyngitis, Roseola, Viral infection, Viral rash | Uncommon |
| Bronchiolitis, Candida nappy rash, Candidiasis, Cellulitis, Infectious croup, Viral gastroenteritis, Hand-foot-mouth disease, Influenza, Pseudocroup, Respiratory infection, Skin infection, Tonsillitis, Varicella$^{+}$ ‡, Viral conjunctivitis | Rare |
| Aseptic meningitis*,<br>Atypical measles, Epididymitis, Herpes zoster*, Infection, Influenza, Measles, Orchitis, Parotitis | Not known |
| **Blood and the lymphatic system disorders** | |
| Leukocytosis, Lymphadenopathy | Rare |
| Lymphadenitis, Regional lymphadenopathy, Thrombocytopenia | Not known |
| **Immune system disorders** | |
| Hypersensitivity | Rare |
| Anaphylactoid reaction, Anaphylaxis and related phenomenon such as Angioneurotic oedema, Facial oedema, and Peripheral oedema, Anaphylaxis in individuals with or without an allergic history | Not known |
| **Metabolism and nutrition disorders** | |
| Anorexia, Decreased appetite | Uncommon |
| Dehydration | Rare |
| **Psychiatric disorders** | |
| Irritability | Common |
| Crying, Insomnia, Sleep disorder | Uncommon |
| Agitation, Apathy, Clinging, Emotional changes, Nervousness, Restlessness | Rare |
| **Nervous system disorders** | |
| Febrile seizure*, Somnolence | Uncommon |

| | |
|---|---|
| Ataxia, Convulsion, Headache, High-pitched crying, Hyperkinesia, Hypersomnia, Lethargy, Tremor | Rare |
| Afebrile convulsions or seizures, Bell's palsy, Cerebrovascular accident, Dizziness, Dream abnormality, Encephalitis*, Encephalopathy*, Guillain-Barré syndrome, Measles inclusion body encephalitis (see section 4.3), Ocular palsies, Paraesthesia, Polyneuritis, Polyneuropathy, Subacute sclerosing panencephalitis*, Syncope, Transverse myelitis, Tremor | Not known |
| **Eye disorders** | |
| Conjunctivitis, Eye discharge, Eyelid inflammation, Eye irritation, Eye swelling, Ocular hyperaemia, Tearing, Visual discomfort | Rare |
| Oedema of the eyelid, Irritation, Optic neuritis, Retinitis, Retrobulbar neuritis | Not known |
| **Ear and labyrinth disorders** | |
| Ear pain | Rare |
| Nerve deafness | Not known |
| **Vascular disorders** | |
| Flushing, Pallor | Rare |
| Extravasation | Not known |
| **Respiratory, thoracic, and mediastinal disorders** | |
| Cough, Nasal congestion, Respiratory congestion, Rhinorrhoea | Uncommon |
| Asthma, Pulmonary congestion, Sinus disorder, Sneezing, Wheezing | Rare |
| Bronchial spasm, Bronchitis, Epistaxis, Pneumonitis (see section 4.3), Pneumonia, Pulmonary congestion, Rhinitis, Sinusitis, Sore throat | Not known |
| **Gastrointestinal disorders** | |
| Diarrhoea, Vomiting | Common |
| Abdominal pain upper, Abnormal faeces, Constipation, Flatulence, Nausea, Salivation increase, Stomatitis, Teething | Rare |
| Abdominal pain, Haematochezia, Mouth ulcer | Not known |
| **Skin and subcutaneous tissue disorders** | |
| Measles-like rash‡, Rash, Varicella-like rash‡ | Common |
| Dermatitis (including contact, atopic, and diaper rash), Heat rash, Rubella-like rash‡, Urticaria, Viral exanthema, Eczema, Erythema | Uncommon |
| Acne, Clammy skin, Exfoliative dermatitis, Drug eruption, Exanthema, Livedo reticularis, Papular rash, Pruritus, Skin discoloration, Skin lesion, Zosteriform rash | Rare |
| Erythema multiforme, Henoch-Schönlein purpura, Herpes simplex, Impetigo, Panniculitis, Purpura, Skin induration, Stevens-Johnson syndrome, Sunburn | Not known |
| **Musculoskeletal, connective tissue and bone disorders** | |
| Arm pain, Musculoskeletal stiffness | Rare |
| Arthritis and/or arthralgia (usually transient and rarely chronic)* , Musculoskeletal pain, Myalgia, Pain of the hip, leg, or neck, Swelling | Not known |
| **General disorders and administration site conditions** | |
| Fever‡, Erythema‡ or Pain/Tenderness/Soreness‡ at | Very common |

| | |
|---|---|
| the injection site | |
| Ecchymosis or Swelling‡ at the injection site, injection-site rash‡ | Common |
| Asthenia/fatigue, Injection-site haemorrhage, Injection-site induration or warmth, Injection-site mass, Malaise | Uncommon |
| Influenza-like illness, Injection-site desquamation, Injection-site discoloration, Injection-site pruritus, Injection-site rash non-specific, Injection-site reaction, Injection-site scar, Hyperthermia, Pain, Pain/Tenderness/Soreness | Rare |
| Injection site complaints (Burning and/or Stinging of short duration, Eczema, Oedema/Swelling, Hive-like rash, Hematoma, Induration, Lump, Vesicles, Wheal and Flare), Inflammation, Lip abnormality, Papillitis, Roughness/Dryness, Stiffness, Trauma, Varicella-like rash, Venipuncture site haemorrhage, Warm sensation, Warm to touch | Not known |
| **Investigations** | |
| Weight loss | Rare |
| **Injury and poisoning, and procedural complications** | |
| Contusion, Non-venomous bite/sting | Rare |
| **Social circumstances** | |
| Activities of daily living impaired | Rare |

+ Varicella caused by vaccine strain was observed in post-marketing use with Varicella Vaccine live (Oka/Merck).
***** See section c

c. Description of selected adverse reactions

Aseptic meningitis
Cases of aseptic meningitis have been reported following measles, mumps, and rubella vaccination. Although a causal relationship between other strains of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Febrile seizures
Febrile seizures have been reported in children receiving ProQuad. Consistent with clinical study data on the timing of fever and measles-like rash, a post-marketing observational study in children 12 to 60 months of age revealed an approximate two-fold increase (0.70 per 1000 vs. 0.32 per 1000 children) in the risk of febrile seizures in the 5- to 12-day timeframe after a first dose of ProQuad (N=31,298) compared with concomitant administration of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck) (N=31,298).These data suggest one additional case of febrile seizure per 2600 children vaccinated with ProQuad compared with separate administration of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck). These data were confirmed by a post marketing observational study sponsored by the U.S. Centers for Disease Control and Prevention. In the 30-day timeframe following vaccination, no increased risk of febrile seizures was observed (see section 5.1).

Encephalitis and encephalopathy
Encephalitis and encephalopathy (excluding subacute sclerosing panencephalitis [SSPE]) have been reported approximately once for every 3 million doses of the measles-containing vaccines manufactured by Merck & Co., Inc. Post-marketing surveillance of the more than 428 million doses that have been distributed worldwide (1978 to 2005) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. In no case has it been shown

conclusively that reactions were actually caused by the vaccine; however, the data suggest the possibility that some of these cases may have been caused by measles vaccines.

SSPE
There is no evidence that measles vaccine can cause SSPE. There have been reports of SSPE in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. The results of a retrospective case-controlled study conducted by the US Centers for Disease Control and Prevention show that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent risk of SSPE.

Arthralgia and/or arthritis
Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and gender, being greatest in adult females and least in prepubertal children. Following vaccination in children, reactions in joints are generally uncommon (0 to 3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (12 to 20%), and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and adult women. Even in older women (35 to 45 years), these reactions are generally well tolerated and rarely interfere with normal activities.

Chronic arthritis
Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Cases of herpes zoster in clinical studies
In a clinical trial, 2 cases of herpes zoster were reported in 2108 healthy subjects 12 through 23 months of age who were vaccinated with one dose of ProQuad and followed for 1 year. Both cases were unremarkable and no sequelae were reported.

Active surveillance data in children vaccinated with Varicella Vaccine live (Oka/Merck) 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. These surveillance data actually suggest that varicella-vaccinated children may have a lower risk of herpes zoster. However, the long term effect of varicella vaccination on the incidence of herpes zoster is unknown at present. There are no long-term data currently available with ProQuad (see section 5.1).

Transmission
Based on isolated case reports from post-marketing surveillance for Varicella Vaccine live (Oka/Merck), the possibility exists that varicella vaccine virus may rarely be transmitted to contacts of recipients of ProQuad who develop or do not develop a varicella-like rash (see section 4.4).

### 4.9 Overdose

No case of overdose has been reported.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral Vaccine; ATC code: J07BD54.

Efficacy

Formal studies to evaluate the efficacy of ProQuad have not been performed. However, the efficacy of Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. has been demonstrated in numerous studies.

Efficacy of the measles, mumps, and rubella components of ProQuad was previously established in a series of double-blind controlled field trials with the monovalent vaccines manufactured by Merck & Co., Inc., which demonstrated a high degree of protective efficacy. In these studies seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases. ProQuad elicits rates of antibody responses against measles, mumps, and rubella similar to those observed after vaccination with the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.

More than 518 million doses of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. have been distributed worldwide (1978 to 2007). Widespread use of a 2-dose vaccination schedule in the United States and countries such as Finland and Sweden has led to a >99% reduction in the incidence of each of the 3 targeted diseases.

In combined clinical trials of a single dose of Varicella Vaccine live (Oka/Merck) in healthy children, the protective efficacy of the vaccine against all severities of varicella disease ranged from 81% to 100%. In a large case-control study, the vaccine was estimated to be 85% effective against all forms of varicella and 97% effective against moderately severe and severe disease.

In a study comparing 1 dose (N=1114) to 2 doses (N=1102) of Varicella Vaccine live (Oka/Merck), the estimated vaccine efficacy against all severities of varicella disease for the 10-year observation period was 94% for 1 dose and 98% for 2 doses ($p<0.001$). Over the 10-year observation period, the cumulative rate of varicella 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 of vaccine were mild.

Antibody responses against varicella virus ≥5 gpELISA Units/ml in the glycoprotein enzyme-linked immunosorbent assay (gpELISA, a highly sensitive assay which is not commercially available) have been shown to be highly correlated with long-term protection. Clinical studies have shown that immunization with ProQuad elicits rates of antibody responses against varicella virus ≥5 gpELISA Units/ml similar to those observed after vaccination with Varicella Vaccine live (Oka/Merck).

Immunogenicity

Immunogenicity was studied in children 12 through 23 months of age with a negative clinical history of measles, mumps, rubella, and varicella who participated in 5 randomized clinical trials. The immunogenicity of the current refrigerator-stable formulation was shown to be similar to the immunogenicity of the earlier formulation of ProQuad six weeks after a single dose of the vaccine. The immunogenicity of a single dose of an earlier formulation of ProQuad was comparable to the immunogenicity of a single dose of its individual component vaccines (Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.), currently used in routine vaccination in some countries.

Clinical trials involving 6987 subjects who received ProQuad demonstrated detectable immune responses to measles, mumps, rubella, and varicella in a high proportion of individuals. The presence of detectable antibody was assessed by an appropriately sensitive enzyme-linked immunosorbent assay (ELISA) for measles, mumps (wild-type and vaccine-type strains), and rubella, and by gpELISA for varicella. Following a single dose of ProQuad, the vaccine response rates were 97.7% for measles, 96.3% to 98.8% for mumps, and 98.8% for rubella. While the seroconversion rate for varicella was uniformly high (97.9% to 99.8% across all studies), seroconversion has not been shown to correlate well with protection. The vaccine response rate was 90.9% (range 80.8% to 94.5%) for varicella based on a post-vaccination antibody titer ≥5 gpELISA units/ml (an antibody titer that has been shown to be highly correlated with long-term protection). These results were similar to the immune response rates induced by concomitant administration of a single dose of Varicella Vaccine live

(Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. at separate injection sites.

Evaluation of immunogenicity in children from 9 to 12 months of age at the time of first dose
A clinical study was conducted with ProQuad 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), high seroprotection rates of >99% were elicited to mumps, rubella, and varicella post-dose 2, regardless of the age of the vaccinees at the first dose. After 2 doses, the seroprotection rates against measles were 98.1% when the first dose was given at 11 months, compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective met). After two doses, the seroprotection rates against measles were 94.6% when the first dose was given at 9 months, compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective not met).

The seroprotection rates to measles, mumps, rubella, and varicella 6 weeks post-dose 1 and 6 weeks post-dose 2, for the Full Analysis Set are given in the following table.

| **Valence (seroprotection level)** | **Time point** | **Dose 1 at 9 months / Dose 2 at 12 months N = 527** | **Dose 1 at 11 months / Dose 2 at 14 months N = 480** | **Dose 1 at 12 months / Dose 2 at 15 months N = 466** |
|---|---|---|---|---|
| | | **Seroprotection rates [95% CI]** | **Seroprotection rates [95% CI]** | **Seroprotection rates [95% CI]** |
| **Measles** (titre ≥255 mIU/mL) | **Post-dose 1** | 72.3% [68.2; 76.1] | 87.6% [84.2; 90.4] | 90.6% [87.6; 93.1] |
| | **Post-dose 2** | 94.6% [92.3; 96.4] | 98.1% [96.4; 99.1] | 98.9% [97.5; 99.6] |
| **Mumps** (titre ≥10 ELISA Ab units/mL) | **Post-dose 1** | 96.4% [94.4; 97.8] | 98.7% [97.3; 99.5] | 98.5% [96.9; 99.4] |
| | **Post-dose 2** | 99.2% [98.0; 99.8] | 99.6% [98.5; 99.9] | 99.3% [98.1; 99.9] |
| **Rubella** (titre ≥10 IU/mL) | **Post-dose 1** | 97.3% [95.5; 98.5] | 98.7% [97.3; 99.5] | 97.8% [96.0; 98.9] |
| | **Post-dose 2** | 99.4% [98.3; 99.9] | 99.4% [98.1; 99.9] | 99.6% [98.4; 99.9] |
| **Varicella** (titre ≥5 gp ELISA units/mL) | **Post-dose 1** | 93.1% [90.6; 95.1] | 97.0% [95.1; 98.4] | 96.5% [94.4; 98.0] |
| | **Post-dose 2** | 100% [99.3; 100] | 100% [99.2; 100] | 100% [99.2; 100] |

The post-dose 2 geometric mean titres (GMTs) against mumps, rubella, and varicella were comparable across all age categories, while the GMTs against measles were lower in subjects who received the first dose at 9 months of age as compared to subjects who received the first dose at 11 or 12 months of age.

Children who received a second dose of ProQuad
In 2 clinical trials, 1035 subjects were administered a second dose of ProQuad approximately 3 months after the first dose. The vaccine response rates were 99.4% for measles, 99.9% for mumps, 98.3% for rubella, and 99.4% for varicella (≥5 gpELISA Units/ml). The geometric mean titers (GMTs) following the second dose of ProQuad increased approximately 2 fold each for measles, mumps, and rubella, and approximately 41 fold for varicella (for safety information, see section 4.8).

Children who received ProQuad at 4 through 6 years of age after primary vaccination with Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.

The immunogenicity and safety of ProQuad were evaluated in a clinical trial involving 799 subjects 4 through 6 years of age who had received Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. at least 1 month prior to study entry. Following the dose of ProQuad, GMTs for measles, mumps, rubella, and varicella were similar to those following a second dose of Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. administered concomitantly at separate injection sites. Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. given concomitantly with placebo (for safety information, see section 4.8).

Persistence of Immune Response

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2108 subjects who were involved in 1 clinical trial. The antibody persistence rates 1 year postvaccination in recipients of a single dose of ProQuad were 98.9% (1722/1741) for measles, 96.7% (1676/1733) for mumps, 99.6% (1796/1804) for rubella, and 97.5% (1512/1550) for varicella (≥5 gpELISA Units/ml).

Experience with the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. demonstrates that antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination. In clinical studies involving healthy subjects who received 1 dose of Varicella Vaccine live (Oka/Merck), detectable varicella antibodies were present in most individuals tested for up to 10 years postvaccination.

Observational studies of long-term effectiveness of varicella vaccine

Surveillance data from two U.S. observational effectiveness studies confirmed that widespread varicella vaccination reduces the risk of varicella by approximately 90% and that protection is maintained over at least 15 years both in vaccinated and unvaccinated individuals. These 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. 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 hospitalization rates was observed in all age groups.

Post-Marketing Observational Safety Surveillance Study

Safety was evaluated in an observational study that included 69,237 children vaccinated with ProQuad 12 months to 12 years old and 69,237 matched children in a historical comparison group who were vaccinated concomitantly with the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck). In addition to assessing the incidence of febrile seizures occurring within 30 days after the first dose (see section 4.8), the study also assessed the general safety of ProQuad in the 30-day period after the first or second dose. Other than

the increase in febrile seizure after the first dose, no safety concerns after the first or second dose were identified.

### 5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

### 5.3 Preclinical safety data

Traditional non-clinical studies were not performed, but there are no non-clinical 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
Sodium chloride
Sorbitol
Monosodium glutamate
Sodium phosphate
Sodium bicarbonate
Potassium phosphate
Potassium chloride
Medium 199 with Hanks' Salts
Minimum Essential Medium, Eagle (MEM)
Neomycin
Phenol red
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)
Urea

Solvent
Water for injections.

### 6.2 Incompatibilities

In the absence of compatibility studies, the vaccine must not be mixed with other medicinal products.

### 6.3 Shelf life

18 months.

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). Store in the original package in order to protect from light.

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

### 6.5 Nature and contents of container

Powder in a vial (glass) with a stopper (butyl rubber) and solvent in a vial (glass) with stopper (chlorobutyl rubber) in a pack size of 1 and 10.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

To reconstitute the vaccine, use only the solvent supplied, because it is free of preservatives or other antiviral substances, which might inactivate the vaccine. ProQuad, when reconstituted, is clear pale yellow to light pink liquid.

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

ProQuad must not be mixed in a syringe with other vaccines.

Reconstitution instructions
Withdraw the entire volume of solvent into a syringe. Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

**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.**

The reconstituted vaccine must not be used if any particulate matter is noted or if the appearance of the vaccine differs from that described above.

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

## 7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8 rue Jonas Salk
F-69007 Lyon
France

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/05/323/001
EU/1/05/323/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 April 2006
Date of latest renewal: 10 April 2011

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection in a pre-filled syringe.
Measles, mumps, rubella and varicella vaccine (live).

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 ml) contains:

Measles virus[1] Enders' Edmonston strain (live, attenuated)..... not less than 3.00 $\log_{10}$ $CCID_{50}$*
Mumps virus[1] Jeryl Lynn™ (Level B) strain (live, attenuated)... not less than 4.30 $\log_{10}$ $CCID_{50}$*
Rubella virus[2] Wistar RA 27/3 strain (live, attenuated)..... not less than 3.00 $\log_{10}$ $CCID_{50}$*
Varicella virus[3] Oka/Merck strain (live, attenuated) ..... not less than 3.99 $\log_{10}$ PFU**

*50% cell culture infectious dose
**plaque-forming units

([1]) Produced in chick embryo cells.
([2]) Produced in human diploid lung (WI-38) fibroblasts.
([3]) Produced in human diploid (MRC-5) cells.

This vaccine contains a trace amount of neomycin. See section 4.3.

Excipients with known effect:
Sorbitol 16 mg
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection in a pre-filled syringe.

Before reconstitution, the powder is a white to pale yellow compact crystalline cake and the solvent is a clear colourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ProQuad is indicated for simultaneous vaccination against measles, mumps, rubella, and varicella in individuals from 12 months of age.

ProQuad can be administered to individuals from 9 months of age under special circumstances (e.g., to conform with national vaccination schedules, outbreak situations, or travel to a region with high prevalence of measles; see sections 4.2, 4.4, and 5.1).

### 4.2 Posology and method of administration

Posology

ProQuad should be used in accordance to official recommendations.

- Individuals 12 months of age and older

Individuals from 12 months of age should receive two doses of ProQuad or a single dose of ProQuad followed by a second dose of a monovalent varicella vaccine to ensure optimal protection against varicella (see section 5.1). At least one month must elapse between the first and second dose of any live viral attenuated vaccine. It is preferred that the second dose be administered within three months following the first dose.

- Individuals between 9 and 12 months of age
  Immunogenicity and safety data show that ProQuad can be administered to individuals between 9 and 12 months of age, under special circumstances (e.g., in accordance with official recommendations or when early protection is considered necessary). In such cases, individuals should receive a second dose of ProQuad, given a minimum of 3 months apart, to ensure optimal protection against measles and varicella (see sections 4.4 and 5.1).

- Individuals less than 9 months of age
  ProQuad is not indicated in this subset of the paediatric population. The safety and efficacy of ProQuad in children under 9 months of age have not been established.

ProQuad may be used as the second dose in individuals who have previously received measles, mumps, and rubella vaccine and varicella vaccine.

Method of administration
The vaccine is to be injected by the subcutaneous route in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

**DO NOT INJECT INTRAVASCULARLY.**

## 4.3 Contraindications

History of hypersensitivity to any varicella vaccine or measles, mumps, or rubella vaccine, to any of the excipients, or to neomycin, which may be present as trace residues (see sections 2, 4.4 and 6.1).

Blood dyscrasias, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the haematopoietic and lymphatic system.

Current immunosuppressive therapy (including high doses of corticosteroids). ProQuad is not contraindicated in individuals who are receiving topical or low-dose parenteral corticosteroids (e.g. for asthma prophylaxis or replacement therapy).

Severe humoral or cellular (primary or acquired) immunodeficiency, e.g., severe combined immunodeficiency, agammaglobulinemia 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 section 4.4).

In severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine, measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported.

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

Active untreated tuberculosis. Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine. No studies have been reported to date on the effect of measles virus vaccines on children with untreated tuberculosis.

Vaccination should be postponed during any illness with fever >38.5°C.

Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

## 4.4 Special warnings and precautions for use

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Additionally, live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g. hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination in such cases.

Due caution should be employed in the administration of ProQuad to persons with individual or family history of convulsions, or a history of cerebral injury. The physician should be alert to the temperature elevation that may occur following vaccination (see section 4.8).

Individuals less than 12 months of age who are vaccinated with a measles-containing vaccine during measles outbreaks or for other reasons may fail to respond to the vaccine due to the presence of circulating antibodies of maternal origin and/or immaturity of the immune system (see sections 4.2 and 5.1).

This vaccine contains 16 mg of sorbitol as an excipient. Patients with rare hereditary problems of fructose intolerance should not take this vaccine.

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

Vaccination with ProQuad may not result in protection in all vaccine recipients.

Transmission

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk; however, transmission of the rubella vaccine virus to infants via breast milk has been documented without any evidence of clinical disease (see section 4.6).

There are no reports of transmission of the more attenuated Enders' Edmonston strain of measles virus or the Jeryl Lynn™ strain of mumps virus from vaccine recipients to susceptible contacts.

Post-licensing experience with Varicella Vaccine live (Oka/Merck) suggests that transmission of varicella vaccine virus may rarely occur between healthy vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella, as well as high-risk individuals susceptible to varicella (see section 4.8).

High-risk individuals susceptible to varicella include:

- immunocompromised individuals (see section 4.3),
- pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection,
- newborn infants of mothers without documented positive history of varicella or laboratory evidence of prior infection.

Vaccine recipients should attempt to avoid, whenever possible, close association with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination. In circumstances where contact with high-risk individuals susceptible to varicella is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus.

Thrombocytopenia
In clinical trials, no cases were reported regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad. Cases of thrombocytopenia have been reported in post-marketing experience after primary vaccination with ProQuad. In addition, cases of thrombocytopenia have been reported after primary vaccination or revaccination with measles vaccine; measles, mumps, and rubella vaccine; and varicella vaccine. Post-marketing experience with live measles, mumps, and rubella vaccine indicates that individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia following the first dose of a live measles, mumps, and rubella vaccine may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The risk-to-benefit ratio should be carefully evaluated before considering vaccination with ProQuad in such cases (see section 4.8).

Febrile seizures
In the 5- to 12-day timeframe after the administration of the first dose of quadrivalent measles, mumps, rubella and varicella vaccines in children, an increased risk of febrile seizure was observed compared to concomitant administration of measles, mumps, rubella and varicella vaccines (see sections 4.8 and 5.1).

Other
Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (asymptomatic HIV patients, 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 patients; therefore, some of these patients may acquire measles, mumps, rubella, or varicella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of measles, parotitis, rubella, and varicella.

Post-exposure prophylaxis
No clinical data are available for ProQuad administered after exposure to measles, mumps, rubella, or varicella. However, post-exposure prophylaxis for varicella and measles has been demonstrated with Varicella Vaccine live (Oka/Merck) and the measles-containing vaccines manufactured by Merck & Co., Inc., respectively.

Interference with laboratory tests: see section 4.5.

## 4.5 Interaction with other medicinal products and other forms of interaction

At least 1 month should elapse between receipt of a live virus vaccine and ProQuad.

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad (see section 4.4).

Do not give immunoglobulin (IG) or Varicella Zoster Immune Globulin (VZIG) concomitantly with ProQuad.

Administration of immune globulins concomitantly with ProQuad may interfere with the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of immune globulins (IG). However, the appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (e.g. 5 months for VZIG).

Administration of varicella zoster virus antibody-containing blood products, including VZIG or other immune globulin preparations, within 1 month following a dose of ProQuad 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 ProQuad unless considered to be essential.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either any time before, simultaneously with, or at least 4 to 6 weeks after immunization with ProQuad.

Concomitant use with other vaccines:
Clinical studies have demonstrated that ProQuad can be given simultaneously (but at separate injection sites) with Prevenar and/or hepatitis A vaccine, or with monovalent or combination vaccines comprised of diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, or hepatitis B antigen. In these clinical studies, it was demonstrated that the immune responses were unaffected. The safety profiles of the administered vaccines were comparable (see section 4.8).

There are insufficient data to support the use of ProQuad with any other vaccines.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnant women should not be vaccinated with ProQuad.

Studies have not been conducted with ProQuad in pregnant women. It is not known whether ProQuad can cause foetal harm when administered to a pregnant woman or 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
Studies have shown that breast-feeding postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection, none had symptomatic disease. There is no evidence that varicella vaccine virus is excreted in breast milk. It is not known whether measles or mumps vaccine virus is secreted in human milk. Therefore, caution should be exercised when considering whether to administer ProQuad to a breast-feeding woman.

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

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machinery have been performed. ProQuad is expected to have no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

a. Summary of the safety profile
In 5 clinical trials, ProQuad was administered without concomitant vaccines to 6038 children 12 through 23 months of age. The children in these studies received either the current refrigerator-stable formulation or an earlier formulation of ProQuad. Children in these studies were monitored for six weeks post vaccination. The safety profiles were comparable for the two different formulations after a single dose. The only vaccine-related systemic adverse reactions reported at a significantly greater rate in individuals who received the earlier formulation of ProQuad compared to individuals who received the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. and Varicella Vaccine live (Oka/Merck) were fever (≥39.4°C rectal equivalent or abnormal) and measles-like rash. Both fever and measles-like rash usually occurred within 5 to 12 days following the vaccination, were of short duration and resolved with no long-term sequelae. Pain/tenderness/soreness at the injection site was reported at a statistically lower rate in individuals who received ProQuad.

The only vaccine related injection-site adverse reaction that was more frequent among recipients of ProQuad than among recipients of Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co. Inc. was rash at the injection site.

Following ProQuad given alone in 7 clinical trials, the observed rates of fever (≥39.4°C rectal equivalent) ranged from 10.1% to 39.4%. In comparison, following ProQuad given concomitantly with Prevenar and/or hepatitis A vaccine in 3 clinical trials, the observed rates of reported fever (≥39.4°C rectal equivalent) ranged from 15.2% to 27.2%.

In a clinical trial of ProQuad administered concomitantly with Infanrix Hexa, the rates of fever (≥38.0°C rectal equivalent) were 69.3% following concomitant administration, 61.1% following ProQuad alone, and 57.3% following Infanrix Hexa alone; the rates of fever (≥39.4°C rectal equivalent) were 22.6% following concomitant administration, 20.5% following ProQuad alone, and 15.9% following Infanrix Hexa alone.

The overall safety profile of ProQuad was comparable whether it was administered concomitantly or alone.

Children who received a second dose of ProQuad
In eight clinical studies, the overall rates of adverse reactions after a second dose of ProQuad were generally similar to, or lower than, those seen with the first dose. In three of these studies, the rates of injection-site erythema and swelling were statistically significantly higher after the second dose than after the first dose; however, in the remaining five studies, the rates of each of these reactions were similar after the first and second dose. The fever rate in all eight studies was lower after the second dose than after the first dose.

Children who received ProQuad at 4 through 6 years of age after primary immunization with Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.
The rates and types of adverse reactions seen in the study group that received ProQuad were generally similar to those seen in the groups that received Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. (see section 5.1 for study description).

No specific studies have been conducted in individuals from 2 years of age who had not previously received measles, mumps, rubella, and varicella vaccines.

The most common adverse events reported with the use of ProQuad were: injection-site reactions including pain/tenderness/soreness, redness, swelling or bruising; fever (≥39.4°C rectal equivalent); irritability; rash (including measles-like rash, varicella-like rash, and injection-site rash); upper respiratory infection; vomiting and diarrhoea.

b. Tabulated summary of adverse reactions

The following adverse reactions were reported as vaccine related by the investigator in individuals after a single dose of ProQuad. Several adverse events were solicited in the clinical studies and are designated with the symbol (‡). Additionally, other adverse experiences have been reported with post-marketing use of ProQuad and/or in clinical studies and post-marketing use of either the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., the monovalent component vaccines of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., or Varicella Vaccine live (Oka/Merck). These adverse effects are listed below without regard to causality or frequency (frequency *not known*).

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000), including isolated reports; not known (cannot be estimated from the available data)

| Adverse reactions | Frequency |
|---|---|
| **Infections and infestations** | |
| Upper respiratory infection | Common |
| Ear infection, Gastroenteritis, Nasopharyngitis, Otitis media, Pharyngitis, Roseola, Viral infection, Viral rash | Uncommon |
| Bronchiolitis, Candida nappy rash, Candidiasis, Cellulitis, Infectious croup, Viral gastroenteritis, Hand-foot-mouth disease, Influenza, Pseudocroup, Respiratory infection, Skin infection, Tonsillitis, Varicella$^{+}$ ‡, Viral conjunctivitis | Rare |
| Aseptic meningitis*****, Atypical measles, Epididymitis, Herpes zoster*****, Infection, Influenza, Measles, Orchitis, Parotitis. | Not known |
| **Blood and the lymphatic system disorders** | |
| Leukocytosis, Lymphadenopathy | Rare |
| Lymphadenitis, Regional lymphadenopathy, Thrombocytopenia | Not known |
| **Immune system disorders** | |
| Hypersensitivity | Rare |
| Anaphylactoid reaction, Anaphylaxis and related phenomenon such as Angioneurotic oedema, Facial oedema, and Peripheral oedema, Anaphylaxis in individuals with or without an allergic history | Not known |
| **Metabolism and nutrition disorders** | |
| Anorexia, Decreased appetite | Uncommon |
| Dehydration | Rare |
| **Psychiatric disorders** | |
| Irritability | Common |
| Crying, Insomnia, Sleep disorder | Uncommon |
| Agitation, Apathy, Clinging, Emotional changes, Nervousness, Restlessness | Rare |
| **Nervous system disorders** | |
| Febrile seizure*, Somnolence | Uncommon |

| | |
|---|---|
| Ataxia, Convulsion, Headache, Highpitched crying, Hyperkinesia, Hypersomnia, Lethargy, Tremor | Rare |
| Afebrile convulsions or seizures, Bell's palsy, Cerebrovascular accident, Dizziness, Dream abnormality, Encephalitis*, Encephalopathy*, Guillain-Barré syndrome, Measles inclusion body encephalitis (see section 4.3), Ocular palsies, Paraesthesia, Polyneuritis, Polyneuropathy, Subacute sclerosing panencephalitis*, Syncope, Transverse myelitis, Tremor | Not known |
| **Eye disorders** | |
| Conjunctivitis, Eye discharge, Eyelid inflammation, Eye irritation, Eye swelling, Ocular hyperaemia, Tearing, Visual discomfort | Rare |
| Oedema of the eyelid, Irritation, Optic neuritis, Retinitis, Retrobulbar neuritis | Not known |
| **Ear and labyrinth disorders** | |
| Ear pain | Rare |
| Nerve deafness | Not known |
| **Vascular disorders** | |
| Flushing, Pallor | Rare |
| Extravasation | Not known |
| **Respiratory, thoracic, and mediastinal disorders** | |
| Cough, Nasal congestion, Respiratory congestion, Rhinorrhoea | Uncommon |
| Asthma, Pulmonary congestion, Sinus disorder, Sneezing, Wheezing | Rare |
| Bronchial spasm, Bronchitis, Epistaxis, Pneumonitis (see section 4.3), Pneumonia, Pulmonary congestion, Rhinitis, Sinusitis, Sore throat | Not known |
| **Gastrointestinal disorders** | |
| Diarrhoea, Vomiting | Common |
| Abdominal pain upper, Abnormal faeces, Constipation, Flatulence, Nausea, Salivation increase, Stomatitis, Teething | Rare |
| Abdominal pain, Haematochezia, Mouth ulcer | Not known |
| **Skin and subcutaneous tissue disorders** | |
| Measles-like rash‡, Rash, Varicella-like rash‡ | Common |
| Dermatitis (including contact, atopic, and diaper rash), Heat rash, Rubella-like rash‡, Urticaria, Viral exanthema, Eczema, Erythema | Uncommon |
| Acne, Clammy skin, Exfoliative dermatitis, Drug eruption, Exanthema, Livedo reticularis, Papular rash, Pruritus, Skin discoloration, Skin lesion, Zosteriform rash | Rare |
| Erythema multiforme, Henoch-Schönlein purpura, Herpes simplex, Impetigo, Panniculitis, Purpura, Skin induration, Stevens-Johnson syndrome, Sunburn | Not known |
| **Musculoskeletal, connective tissue and bone disorders** | |
| Arm pain, Musculoskeletal stiffness | Rare |
| Arthritis and/or arthralgia (usually transient and rarely chronic) *****, Musculoskeletal pain, Myalgia, Pain of the hip, leg, or neck, Swelling | Not known |
| **General disorders and administration site conditions** | |
| Fever ‡, Erythema‡ or Pain/Tenderness/Soreness‡ at | Very common |

| | |
|---|---|
| the injection site | |
| Ecchymosis or Swelling‡ at the injection site, injection-site rash‡ | Common |
| Asthenia/fatigue, Injection-site haemorrhage, Injection-site induration or warmth, Injection-site mass, Malaise | Uncommon |
| Influenza-like illness, Injection-site desquamation, Injection-site discoloration, Injection-site pruritus, Injection-site rash non-specific, Injection-site reaction, Injection-site scar, Hyperthermia, Pain, Pain/Tenderness/Soreness | Rare |
| Injection site complaints (Burning and/or Stinging of short duration, Eczema, Oedema/Swelling, Hive-like rash, Hematoma, Induration, Lump, Vesicles, Wheal and Flare), Inflammation, Lip abnormality, Papillitis, Roughness/Dryness, Stiffness, Trauma, Varicella-like rash, Venipuncture site haemorrhage, Warm sensation, Warm to touch | Not known |
| **Investigations** | |
| Weight loss | Rare |
| **Injury and poisoning, and procedural complications** | |
| Contusion, Non-venomous bite/sting | Rare |
| **Social circumstances** | |
| Activities of daily living impaired | Rare |

+ Varicella caused by vaccine strain was observed in post-marketing use with Varicella Vaccine live (Oka/Merck).
***** See section c

c. Description of selected adverse reactions

Aseptic meningitis
Cases of aseptic meningitis have been reported following measles, mumps, and rubella vaccination. Although a causal relationship between other strains of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Febrile seizures
Febrile seizures have been reported in children receiving ProQuad. Consistent with clinical study data on the timing of fever and measles-like rash, a post-marketing observational study in children 12 to 60 months of age revealed an approximate two-fold increase (0.70 per 1000 vs. 0.32 per 1000 children) in the risk of febrile seizures in the 5- to 12-day timeframe after a first dose of ProQuad (N=31,298) compared with concomitant administration of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck) (N=31,298). These data suggest one additional case of febrile seizure per 2600 children vaccinated with ProQuad compared with separate administration of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck). These data were confirmed by a post marketing observational study sponsored by the U.S. Centers for Disease Control and Prevention.
In the 30-day timeframe following vaccination, no increased risk of febrile seizures was observed (see section 5.1).

Encephalitis and encephalopathy
Encephalitis and encephalopathy (excluding subacute sclerosing panencephalitis [SSPE]) have been reported approximately once for every 3 million doses of the measles-containing vaccines manufactured by Merck & Co., Inc. Post-marketing surveillance of the more than 428 million doses that have been distributed worldwide (1978 to 2005) indicates that serious adverse events such as

encephalitis and encephalopathy continue to be rarely reported. In no case has it been shown conclusively that reactions were actually caused by the vaccine; however, the data suggest the possibility that some of these cases may have been caused by measles vaccines.

SSPE
There is no evidence that measles vaccine can cause SSPE. There have been reports of SSPE in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. The results of a retrospective case-controlled study conducted by the US Centers for Disease Control and Prevention show that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent risk of SSPE.

Arthralgia and/or arthritis
Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and gender, being greatest in adult females and least in prepubertal children. Following vaccination in children, reactions in joints are generally uncommon (0 to 3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (12 to 20%), and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and adult women. Even in older women (35 to 45 years), these reactions are generally well tolerated and rarely interfere with normal activities.

Chronic arthritis
Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Cases of herpes zoster in clinical studies
In a clinical trial, 2 cases of herpes zoster were reported in 2108 healthy subjects 12 through 23 months of age who were vaccinated with one dose of ProQuad and followed for 1 year. Both cases were unremarkable and no sequelae were reported.

Active surveillance data in children vaccinated with Varicella Vaccine live (Oka/Merck) 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. These surveillance data actually suggest that varicella-vaccinated children may have a lower risk of herpes zoster. However, the long term effect of varicella vaccination on the incidence of herpes zoster is unknown at present. There are no long-term data currently available with ProQuad (see section 5.1).

Transmission
Based on isolated case reports from post-marketing surveillance for Varicella Vaccine live (Oka/Merck), the possibility exists that varicella vaccine virus may rarely be transmitted to contacts of recipients of ProQuad who develop or do not develop a varicella-like rash (see section 4.4).

### 4.9 Overdose

No case of overdose has been reported.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral Vaccine; ATC code: J07BD54.

Efficacy

Formal studies to evaluate the efficacy of ProQuad have not been performed. However, the efficacy of Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. has been demonstrated in numerous studies.

Efficacy of the measles, mumps, and rubella components of ProQuad was previously established in a series of double-blind controlled field trials with the monovalent vaccines manufactured by Merck & Co., Inc., which demonstrated a high degree of protective efficacy. In these studies seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases. ProQuad elicits rates of antibody responses against measles, mumps, and rubella similar to those observed after vaccination with the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.

More than 518 million doses of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. have been distributed worldwide (1978 to 2007). Widespread use of a 2-dose vaccination schedule in the United States and countries such as Finland and Sweden has led to a >99% reduction in the incidence of each of the 3 targeted diseases.

In combined clinical trials of a single dose of Varicella Vaccine live (Oka/Merck) in healthy children, the protective efficacy of the vaccine against all severities of varicella disease ranged from 81% to 100%. In a large case-control study, the vaccine was estimated to be 85% effective against all forms of varicella and 97% effective against moderately severe and severe disease.

In a study comparing 1 dose (N=1114) to 2 doses (N=1102) of Varicella Vaccine live (Oka/Merck), the estimated vaccine efficacy against all severities of varicella disease for the 10-year observation period was 94% for 1 dose and 98% for 2 doses ($p<0.001$). Over the 10-year observation period, the cumulative rate of varicella 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 of vaccine were mild.

Antibody responses against varicella virus ≥5 gpELISA Units/ml in the glycoprotein enzyme-linked immunosorbent assay (gpELISA, a highly sensitive assay which is not commercially available) have been shown to be highly correlated with long-term protection. Clinical studies have shown that immunization with ProQuad elicits rates of antibody responses against varicella virus ≥5 gpELISA Units/ml similar to those observed after vaccination with Varicella Vaccine live (Oka/Merck).

Immunogenicity

Immunogenicity was studied in children 12 through 23 months of age with a negative clinical history of measles, mumps, rubella, and varicella who participated in 5 randomized clinical trials. The immunogenicity of the current refrigerator-stable formulation was shown to be similar to the immunogenicity of the earlier formulation of ProQuad six weeks after a single dose of the vaccine. The immunogenicity of a single dose of an earlier formulation of ProQuad was comparable to the immunogenicity of a single dose of its individual component vaccines (Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.), currently used in routine vaccination in some countries.

Clinical trials involving 6987 subjects who received ProQuad demonstrated detectable immune responses to measles, mumps, rubella, and varicella in a high proportion of individuals. The presence of detectable antibody was assessed by an appropriately sensitive enzyme-linked immunosorbent assay (ELISA) for measles, mumps (wild-type and vaccine-type strains), and rubella, and by gpELISA for varicella. Following a single dose of ProQuad, the vaccine response rates were 97.7% for measles, 96.3% to 98.8% for mumps, and 98.8% for rubella. While the seroconversion rate for varicella was uniformly high (97.9% to 99.8% across all studies), seroconversion has not been shown to correlate well with protection. The vaccine response rate was 90.9% (range 80.8% to 94.5%) for varicella based on a postvaccination antibody titer ≥5 gpELISA units/ml (an antibody titer that has been shown to be highly correlated with long-term protection). These results were similar to the immune response rates induced by concomitant administration of a single dose of Varicella Vaccine live (Oka/Merck)

and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. at separate injection sites.

Evaluation of immunogenicity in children from 9 to 12 months of age at the time of first dose
A clinical study was conducted with ProQuad 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), high seroprotection rates of >99% were elicited to mumps, rubella, and varicella post-dose 2, regardless of the age of the vaccinees at the first dose. After 2 doses, the seroprotection rates against measles were 98.1% when the first dose was given at 11 months, compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective met). After two doses, the seroprotection rates against measles were 94.6% when the first dose was given at 9 months, compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective not met).

The seroprotection rates to measles, mumps, rubella, and varicella 6 weeks post-dose 1 and 6 weeks post-dose 2, for the Full Analysis Set are given in the following table.

| **Valence (seroprotection level)** | **Time point** | **Dose 1 at 9 months / Dose 2 at 12 months N = 527** | **Dose 1 at 11 months / Dose 2 at 14 months N = 480** | **Dose 1 at 12 months / Dose 2 at 15 months N = 466** |
|---|---|---|---|---|
| | | **Seroprotection rates [95% CI]** | **Seroprotection rates [95% CI]** | **Seroprotection rates [95% CI]** |
| **Measles** (titre ≥255 mIU/mL) | **Post-dose 1** | 72.3% [68.2; 76.1] | 87.6% [84.2; 90.4] | 90.6% [87.6; 93.1] |
| | **Post-dose 2** | 94.6% [92.3; 96.4] | 98.1% [96.4; 99.1] | 98.9% [97.5; 99.6] |
| **Mumps** (titre ≥10 ELISA Ab units/mL) | **Post-dose 1** | 96.4% [94.4; 97.8] | 98.7% [97.3; 99.5] | 98.5% [96.9; 99.4] |
| | **Post-dose 2** | 99.2% [98.0; 99.8] | 99.6% [98.5; 99.9] | 99.3% [98.1; 99.9] |
| **Rubella** (titre ≥10 IU/mL) | **Post-dose 1** | 97.3% [95.5; 98.5] | 98.7% [97.3; 99.5] | 97.8% [96.0; 98.9] |
| | **Post-dose 2** | 99.4% [98.3; 99.9] | 99.4% [98.1; 99.9] | 99.6% [98.4; 99.9] |
| **Varicella** (titre ≥5 gp ELISA units/mL) | **Post-dose 1** | 93.1% [90.6; 95.1] | 97.0% [95.1; 98.4] | 96.5% [94.4; 98.0] |
| | **Post-dose 2** | 100% [99.3; 100] | 100% [99.2; 100] | 100% [99.2; 100] |

The post-dose 2 geometric mean titres (GMTs) against mumps, rubella, and varicella were comparable across all age categories, while the GMTs against measles were lower in subjects who received the first dose at 9 months of age as compared to subjects who received the first dose at 11 or 12 months of age.

Children who received a second dose of ProQuad
In 2 clinical trials, 1035 subjects were administered a second dose of ProQuad approximately 3 months after the first dose. The vaccine response rates were 99.4% for measles, 99.9% for mumps, 98.3% for rubella, and 99.4% for varicella (≥5 gpELISA Units/ml). The geometric mean titers (GMTs) following the second dose of ProQuad increased approximately 2 fold each for measles, mumps, and rubella, and approximately 41 fold for varicella (for safety information, see section 4.8).

Children who received ProQuad at 4 through 6 years of age after primary vaccination with Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.

The immunogenicity and safety of ProQuad were evaluated in a clinical trial involving 799 subjects 4 through 6 years of age who had received Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. at least 1 month prior to study entry. Following the dose of ProQuad, GMTs for measles, mumps, rubella, and varicella were similar to those following a second dose of Varicella Vaccine live (Oka/Merck) and the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. administered concomitantly at separate injection sites. Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. given concomitantly with placebo (for safety information, see section 4.8).

Persistence of Immune Response

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2108 subjects who were involved in 1 clinical trial. The antibody persistence rates 1 year postvaccination in recipients of a single dose of ProQuad were 98.9% (1722/1741) for measles, 96.7% (1676/1733) for mumps, 99.6% (1796/1804) for rubella, and 97.5% (1512/1550) for varicella (≥5 gpELISA Units/ml).

Experience with the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. demonstrates that antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination. In clinical studies involving healthy subjects who received 1 dose of Varicella Vaccine live (Oka/Merck), detectable varicella antibodies were present in most individuals tested for up to 10 years postvaccination.

Observational studies of long-term effectiveness of varicella vaccine

Surveillance data from two U.S. observational effectiveness studies confirmed that widespread varicella vaccination reduces the risk of varicella by approximately 90% and that protection is maintained over at least 15 years both in vaccinated and unvaccinated individuals. These 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. 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 hospitalization rates was observed in all age groups.

Post-Marketing Observational Safety Surveillance Study

Safety was evaluated in an observational study that included 69,237 children vaccinated with ProQuad 12 months to 12 years old and 69,237 matched children in a historical comparison group who were vaccinated concomitantly with the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck). In addition to assessing the incidence of febrile seizures occurring within 30 days after the first dose (see section 4.8), the study also assessed the general safety of ProQuad in the 30-day period after the first or second dose. Other than

the increase in febrile seizure after the first dose, no safety concerns after the first or second dose were identified.

### 5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

### 5.3 Preclinical safety data

Traditional non-clinical studies were not performed, but there are no non-clinical 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
Sodium chloride
Sorbitol
Monosodium glutamate
Sodium phosphate
Sodium bicarbonate
Potassium phosphate
Potassium chloride
Medium 199 with Hanks' Salts
Minimum Essential Medium, Eagle (MEM)
Neomycin
Phenol red
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)
Urea

Solvent
Water for injections.

### 6.2 Incompatibilities

In the absence of compatibility studies, the vaccine must not be mixed with other medicinal products.

### 6.3 Shelf life

18 months.

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). Store in the original package in order to protect from light.

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

## 6.5 Nature and contents of container

Powder in a vial (glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe (glass) with attached needle with plunger stopper (chlorobutyl rubber) and needle shield (natural rubber) in a pack size of 1 and 10.

Powder in a vial (glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber) and tip cap (styrene-butadiene rubber), without needle, in a pack size of 1, 10 and 20.

Powder in a vial (glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber) and tip cap (styrene-butadiene rubber), with one or two unattached needles, in a pack size of 1, 10 and 20.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

To reconstitute the vaccine, use only the solvent supplied, because it is free of preservatives or other antiviral substances, which might inactivate the vaccine. ProQuad, when reconstituted, is clear pale yellow to light pink liquid.

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

ProQuad must not be mixed in a syringe with other vaccines.

Reconstitution instructions
Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

**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.**

The reconstituted vaccine must not be used if any particulate matter is noted or if the appearance of the vaccine differs from that described above.

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

# 7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8 rue Jonas Salk
F-69007 Lyon
France

# 8. MARKETING AUTHORISATION NUMBERS

EU/1/05/323/003
EU/1/05/323/004
EU/1/05/323/005
EU/1/05/323/006

EU/1/05/323/007
EU/1/05/323/008
EU/1/05/323/009
EU/1/05/323/010
EU/1/05/323/011
EU/1/05/323/012
EU/1/05/323/013

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 April 2006
Date of latest renewal: 10 April 2011

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Merck Sharp & Dohme Corp.
Sumneytown Pike
West Point
Pennsylvania 19486
U.S.A.

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme BV
Waarderweg 39, 2031 BN Haarlem
P.O. BOX 581, 2003 PC Haarlem
The Netherlands

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**ProQuad - Powder in vial and solvent in vial - Pack of 1, 10**

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection
Measles, mumps, rubella and varicella vaccine (live)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains (live, attenuated):

Measles virus Enders' Edmonston strain ..... ≥ 3.00 log10 $CCID_{50}$*
Mumps virus Jeryl Lynn™ (Level B) strain ..... ≥ 4.30 $log_{10}$ $CCID_{50}$*
Rubella virus Wistar RA 27/3 strain ..... ≥ 3.00 $log_{10}$ $CCID_{50}$*
Varicella virus Oka/Merck strain ..... ≥ 3.99 $log_{10}$ PFU**

*50% cell culture infectious dose
**plaque-forming units

## 3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection.
Pack of 1 single dose vial (powder) + 1 vial (solvent).
Pack of 10 single dose vials (powder) + 10 vials (solvent).

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Keep the vial of powder in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored between 20°C and 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8 rue Jonas Salk
F-69007 Lyon
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/323/001 - pack of 1
EU/1/05/323/002 - pack of 10

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL OF POWDER**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ProQuad powder for suspension for injection

SC

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

## 6. OTHER

SANOFI PASTEUR MSD SNC

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL OF SOLVENT**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ProQuad
Water for injections

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**ProQuad - Powder in vial and solvent in pre-filled syringe with attached needle - Pack of 1, 10**

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection in a pre-filled syringe
Measles, mumps, rubella and varicella vaccine (live)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains (live, attenuated):

Measles virus Enders' Edmonston strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Mumps virus Jeryl Lynn™ (Level B) strain ..... $\geq 4.30$ $\log_{10}$ $CCID_{50}$*
Rubella virus Wistar RA 27/3 strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Varicella virus Oka/Merck strain ..... $\geq 3.99$ $\log_{10}$ PFU**

*50% cell culture infectious dose
**plaque-forming units

## 3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe.
Pack of 1 single dose vial (powder) + 1 pre-filled syringe with attached needle (solvent).
Pack of 10 single dose vials (powder) + 10 pre-filled syringes with attached needle (solvent).

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Keep the vial of powder in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored between 20°C and 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8 rue Jonas Salk
F-69007 Lyon
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/323/003 – pack of 1
EU/1/05/323/004 – pack of 10

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**ProQuad - Powder in vial and solvent in pre-filled syringe without needle - Pack of 1, 10, 20**

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection in a pre-filled syringe
Measles, mumps, rubella and varicella vaccine (live)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains (live, attenuated):

Measles virus Enders' Edmonston strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Mumps virus Jeryl Lynn™ (Level B) strain ..... $\geq 4.30$ $\log_{10}$ $CCID_{50}$*
Rubella virus Wistar RA 27/3 strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Varicella virus Oka/Merck strain ..... $\geq 3.99$ $\log_{10}$ PFU**

*50% cell culture infectious dose
**plaque-forming units

## 3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe.
Pack of 1 single dose vial (powder) + 1 pre-filled syringe without needle (solvent).
Pack of 10 single dose vials (powder) + 10 pre-filled syringes without needle (solvent).
Pack of 20 single dose vials (powder) + 20 pre-filled syringes without needle (solvent).

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Keep the vial of powder in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored between 20°C and 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8 rue Jonas Salk
F-69007 Lyon
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/323/005 – pack of 1
EU/1/05/323/006 – pack of 10
EU/1/05/323/007 – pack of 20

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**ProQuad - Powder in vial and solvent in pre-filled syringe with 1 unattached needle - Pack of 1, 10, 20**

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection in a pre-filled syringe
Measles, mumps, rubella and varicella vaccine (live)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains (live, attenuated):

Measles virus Enders' Edmonston strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Mumps virus Jeryl Lynn™ (Level B) strain ..... $\geq 4.30$ $\log_{10}$ $CCID_{50}$*
Rubella virus Wistar RA 27/3 strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Varicella virus Oka/Merck strain ..... $\geq 3.99$ $\log_{10}$ PFU**

*50% cell culture infectious dose
**plaque-forming units

## 3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe.
Pack of 1 single dose vial (powder) + 1 pre-filled syringe (solvent)+ 1 unattached needle.
Pack of 10 single dose vials (powder) + 10 pre-filled syringes (solvent)+ 10 unattached needles.
Pack of 20 single dose vials (powder) + 20 pre-filled syringes (solvent)+ 20 unattached needles.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Keep the vial of powder in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored between 20°C and 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8 rue Jonas Salk
F-69007 Lyon
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/323/008 – pack of 1
EU/1/05/323/009 – pack of 10
EU/1/05/323/012 – pack of 20

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**ProQuad - Powder in vial and solvent in pre-filled syringe with 2 unattached needles - Pack of 1, 10, 20**

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection in a pre-filled syringe
Measles, mumps, rubella and varicella vaccine (live)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains (live, attenuated):

Measles virus Enders' Edmonston strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Mumps virus Jeryl Lynn™ (Level B) strain ..... $\geq 4.30$ $\log_{10}$ $CCID_{50}$*
Rubella virus Wistar RA 27/3 strain ..... $\geq 3.00$ $\log_{10}$ $CCID_{50}$*
Varicella virus Oka/Merck strain ..... $\geq 3.99$ $\log_{10}$ PFU**

*50% cell culture infectious dose
**plaque-forming units

## 3. LIST OF EXCIPIENTS

Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in a pre-filled syringe.
Pack of 1 single dose vial (powder) + 1 pre-filled syringe (solvent)+ 2 unattached needles.
Pack of 10 single dose vials (powder) + 10 pre-filled syringes (solvent)+ 20 unattached needles.
Pack of 20 single dose vials (powder) + 20 pre-filled syringes (solvent)+ 40 unattached needles.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated. Keep the vial of powder in the outer carton to protect from light.

After reconstitution, use immediately or within 30 minutes if stored between 20°C and 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Read the package leaflet for disposal of medicines no longer required.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8 rue Jonas Salk
F-69007 Lyon
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/323/010 – pack of 1
EU/1/05/323/011 – pack of 10
EU/1/05/323/013 – pack of 20

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**
**VIAL OF POWDER**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ProQuad powder for suspension for injection
SC

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

## 6. OTHER

SANOFI PASTEUR MSD SNC

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**SYRINGE OF SOLVENT**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ProQuad
Water for injections

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

## 6. OTHER

# B. PACKAGE LEAFLET

**Package Leaflet: Information for the User**

**ProQuad**
**Powder and solvent for suspension for injection**
Measles, mumps, rubella and varicella vaccine (live)

**Read all of this leaflet carefully before you or your child is vaccinated because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This vaccine has been prescribed for you or your child only. Do not pass it on to others.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet**


## 1. What ProQuad is and what it is used for

ProQuad is a vaccine containing measles, mumps, rubella, and varicella (chickenpox) viruses that have been weakened. When a person is given the vaccine, the immune system (the body's natural defences) will make antibodies against the measles, mumps, rubella, and varicella viruses. The antibodies help protect against diseases caused by these viruses.

ProQuad is given to help protect your child against measles, mumps, rubella, and varicella (chickenpox). The vaccine may be administered to persons from 12 months of age.

ProQuad may also be administered to infants from 9 months of age under special circumstances (to conform with national vaccination schedules, outbreak situations, or travel to a region with high prevalence of measles).

Although ProQuad contains live viruses, they are too weak to cause measles, mumps, rubella, or varicella (chickenpox) in healthy people.

## 2. What you need to know before you receive ProQuad

**Do not use ProQuad**

- If the person to be vaccinated is allergic to any of the components of this vaccine (including neomycin or any of the other ingredients listed in **section 6**).
- If the person to be vaccinated has a blood disorder or any type of cancer that affects the immune system.
- If the person to be vaccinated is receiving treatment or taking medications that may weaken the immune system (except low-dose corticosteroid therapy for asthma or replacement therapy).
- If the person to be vaccinated has a weakened immune system because of a disease (including AIDS).
- If the person to be vaccinated has a family history of congenital or hereditary immunodeficiency, unless the immune competence of this person is demonstrated.

- If the person to be vaccinated has active untreated tuberculosis.
- If the person to be vaccinated has any illness with fever higher than 38.5°C; however, low-grade fever itself is not a reason to delay vaccination.
- If the person to be vaccinated is pregnant (in addition, pregnancy should be avoided for 1 month after vaccination, see **Pregnancy and breast-feeding**).

**Warnings and precautions**

If the person to be vaccinated has experienced any of the following, talk to the doctor or pharmacist before ProQuad is given:

- an allergic reaction to eggs or anything that contained egg.
- a history or family history of allergies or of convulsions (fits).
- a side effect after vaccination with measles, mumps, or rubella (in a single vaccine or combined vaccine, such as the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. or ProQuad) that involved easy bruising or bleeding for longer than usual.
- an infection with Human Immunodeficiency Virus (HIV) without showing symptoms of HIV disease. However, vaccination may be less effective than for uninfected persons (see **Do not use ProQuad**).

Once vaccinated, the person vaccinated should attempt to avoid for up to 6 weeks following vaccination, whenever possible, close association with the following individuals:

- Individuals with a lowered resistance to diseases.
- Pregnant women who have either not had chickenpox or have not been vaccinated against chickenpox.
- Newborn infants of mothers who have either not had chickenpox or have not been vaccinated against chickenpox.

Tell your doctor if there is anyone who falls into one of the categories above and is expected to be in contact with the person vaccinated after vaccination.

As with other vaccines, ProQuad may not completely protect all persons who are vaccinated. Also, if the person to be vaccinated has already been exposed to the measles, mumps, rubella, or varicella virus but is not yet ill, ProQuad may not be able to prevent the illness from appearing.

**Other medicines and ProQuad**

Tell your doctor or pharmacist if you or your child are taking or have recently taken any other medicines (or other vaccines).

ProQuad can be given at the same time as other childhood vaccines such as Prevenar, and/or hepatitis A vaccine, or with vaccines containing diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, or hepatitis B. A different place for the injection will be used for each vaccine.

The doctor may delay vaccination for at least 3 months following blood or plasma transfusions, or administration of immune globulin (IG), or varicella zoster immune globulin (VZIG). After vaccination with ProQuad, IG or VZIG should not be given for 1 month, unless your doctor tells you otherwise.

If a tuberculin test is to be performed, it should be done either any time before, simultaneously with, or 4 to 6 weeks after vaccination with ProQuad.

Tell the doctor if your child has recently received a vaccine or if one is scheduled to be given in the near future. The doctor will determine when ProQuad may be given.

The use of salicylates (for example, acetylsalicylic acid, a substance present in many medicines used to relieve pain and lower fever) should be avoided for 6 weeks following vaccination with ProQuad.

**Pregnancy and breast-feeding**

ProQuad should not be given to pregnant females. Females of child-bearing age should take the necessary precautions to avoid pregnancy for 1 month following vaccination.

Persons who are breast-feeding or who intend to breast-feed should tell the doctor. The doctor will decide if ProQuad should be given.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this vaccine.

**ProQuad contains sorbitol.**

If you have been told by your doctor that you or your child has an intolerance to some sugars, inform your doctor before you or your child takes this vaccine.

## 3. How to use ProQuad

ProQuad should be injected under the skin in the upper arm or in the outer thigh.

ProQuad is not to be injected directly into any blood vessel.

ProQuad is given by injection as follows:

- Infants between 9 and 12 months of age:
  ProQuad may be administered from 9 months of age. To ensure optimal protection against chickenpox and measles, two doses of ProQuad should be given at least three months apart.
- Individuals 12 months of age and older:
  To ensure optimal protection against chickenpox, two doses of ProQuad should be given at least one month apart.

The appropriate time and number of injections will be determined by your doctor in accordance with official recommendations.

**Reconstitution instructions intended for medical and healthcare professionals are included at the end of the leaflet**

**If you forget to take ProQuad**

Your doctor will decide when to give the missed dose.

## 4. Possible side effects

Like all vaccines and medicines, this vaccine can cause side effects, although not everybody gets them.

The most common side effects reported with the use of ProQuad were: injection site complaints including pain/tenderness/soreness, redness, swelling or bruising; fever (38.9°C or higher);

irritability; rash (including measles-like rash, varicella-like rash, and injection-site rash); upper respiratory infection; vomiting and diarrhoea.

Other less common side effects have been reported following administration of ProQuad and some of these were serious. These included: allergic reactions (hives); seizures with a fever; cough and bronchiolitis (difficulty breathing with or without cough); and unsteadiness with walking.

Other side effects have been reported with the use of at least one of the following: ProQuad, previous formulations of monovalent and of the combined measles, mumps, and rubella vaccines manufactured by Merck & Co., Inc., or varicella vaccine live (Oka/Merck). These adverse events include: unusual bleeding or bruising under the skin, swelling of the testicles; tingling of the skin, herpes zoster (shingles); inflammation of the brain (encephalitis); severe skin disorders; skin infection; stroke; seizures without a fever; joint pain and/or swelling (which could be transient or chronic); and inflammation of the lung (pneumonia/pneumonitis); varicella (chickenpox).

The doctor has a more complete list of side effects for ProQuad and for the vaccine components for ProQuad (the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. and Varicella Vaccine live (Oka/Merck)).

If you or your child get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

## 5. How to store ProQuad

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the outer carton after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C-8°C).

Keep the vial in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What ProQuad contains

After reconstitution, one dose (0.5 ml) contains:
The active substances are:

Measles virus[1] Enders' Edmonston strain (live, attenuated)..... not less than 3.00 $\log_{10}$ $CCID_{50}$*
Mumps virus[1] Jeryl Lynn™ (Level B) strain (live, attenuated)... not less than 4.30 $\log_{10}$ $CCID_{50}$*
Rubella virus[2] Wistar RA 27/3 strain (live, attenuated)..... not less than 3.00 $\log_{10}$ $CCID_{50}$*
Varicella virus[3] Oka/Merck strain (live, attenuated) ..... not less than 3.99 $\log_{10}$ PFU**

*50% cell culture infectious dose
** plaque-forming units

([1]) Produced in chick embryo cells.
([2]) Produced in human diploid lung (WI-38) fibroblasts.

([3]) Produced in human diploid cells (MRC-5).

The other ingredients are:

Powder
Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, hydrochloric acid and sodium hydroxide.

Solvent
Water for injections.

**What ProQuad looks like and contents of the pack**

The vaccine is a powder for suspension for injection contained in a single-dose vial, which should be mixed with solvent provided with the vial of powder.

ProQuad is available in pack of 1 and pack of 10. Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer Responsible for Batch Release: Merck Sharp and Dohme, B.V., Waarderweg, 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**België/Belgique/Belgien**
Sanofi Pasteur MSD, Tél/Tel: +32.2.726.95.84

**България**
Мерк Шарп и Доум България ЕООД тел.: + 359 2 819 3737

**Česká republika**
Merck Sharp & Dohme s. r. o. Tel: +420.233.010.111

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Sanofi Pasteur MSD, Tlf: +45 23 32 69 29

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Merck Sharp & Dohme OÜ, Tel: +372. 6144 200

**Ελλάδα**
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**España**
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**Ireland**
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**Luxembourg/Luxemburg**
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**Magyarország**
MSD Pharma Hungary Kft, Tel.: + 36.1.888.5300

**Malta**
Merck Sharp & Dohme Cyprus Limited., Tel: 8007 4433 (+356 99917558)

**Nederland**
Sanofi Pasteur MSD, Tel: +31.23.567.96.00

**Norge**
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**Österreich**
Sanofi Pasteur MSD GmbH, Tel: +43 1 890 34 91 14

**Polska**
MSD Polska Sp. z o.o., Tel: +48.22.549.51.00

**Portugal**
Sanofi Pasteur MSD, SA, Tel: +351.21.470.45.50

**România**
Merck Sharp & Dohme Romania S.R.L. Tel: + 4021 529 29 00

**Slovenija**
Merck Sharp & Dohme, inovativna zdravila d.o.o., Tel: +386.1.520.4201

**Ísland**
Sanofi Pasteur MSD, Sími: +32.2.726.95.84

**Italia**
Sanofi Pasteur MSD Spa, Tel: +39.06.664.092.11

**Κύπρος**
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**Latvija**
SIA Merck Sharp & Dohme Latvija, Tel: +371.67364.224

**Lietuva**
UAB Merck Sharp & Dohme, Tel: +370.5.2780.247

**Slovenská republika**
Merck Sharp & Dohme, s. r. o., Tel: +421.2.58282010

**Suomi/Finland**
Sanofi Pasteur MSD, Puh/Tel: +358.9.565.88.30

**Sverige**
Sanofi Pasteur MSD, Tel: +46.8.564.888.60

**United Kingdom**
Sanofi Pasteur MSD Ltd, Tel: +44.1.628.785.291

**This leaflet was last revised in:**

**Other source of information**

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

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**The following information is intended for healthcare professionals only:**

**Reconstitution instructions**

Before mixing with the solvent, the powder vaccine is a white to pale yellow compact crystalline cake. When completely mixed, the vaccine is a clear pale yellow to light pink liquid.

Withdraw the entire volume of solvent into a syringe. Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

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 use the reconstituted vaccine if you notice any particulate matter or if the appearance of the vaccine differs from that described above.

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

**See also section 3 How to use ProQuad.**

**Package Leaflet: Information for the User**

**ProQuad**
**Powder and solvent for suspension for injection in a pre-filled syringe**
Measles, mumps, rubella and varicella vaccine (live)

**Read all of this leaflet carefully before you or your child is vaccinated because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This vaccine has been prescribed for you or your child only. Do not pass it on to others.
- If you get any of the side effects talk to your doctor of pharmacist. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet**


## 1. What ProQuad is and what it is used for

ProQuad is a vaccine containing measles, mumps, rubella, and varicella (chickenpox) viruses that have been weakened. When a person is given the vaccine, the immune system (the body's natural defences) will make antibodies against the measles, mumps, rubella, and varicella viruses. The antibodies help protect against diseases caused by these viruses.

ProQuad is given to help protect your child against measles, mumps, rubella, and varicella (chickenpox). The vaccine may be administered to persons from 12 months of age.

ProQuad may also be administered to infants from 9 months of age under special circumstances (to conform with national vaccination schedules, outbreak situations, or travel to a region with high prevalence of measles).

Although ProQuad contains live viruses, they are too weak to cause measles, mumps, rubella, or varicella (chickenpox) in healthy people.

## 2. What you need to know before you receive ProQuad

**Do not use ProQuad**

- If the person to be vaccinated is allergic to any of the components of this vaccine (including neomycin or any of the other ingredients listed in **section 6**).
- If the person to be vaccinated has a blood disorder or any type of cancer that affects the immune system.
- If the person to be vaccinated is receiving treatment or taking medications that may weaken the immune system (except low-dose corticosteroid therapy for asthma or replacement therapy).
- If the person to be vaccinated has a weakened immune system because of a disease (including AIDS).
- If the person to be vaccinated has a family history of congenital or hereditary immunodeficiency, unless the immune competence of this person is demonstrated.

- If the person to be vaccinated has active untreated tuberculosis.
- If the person to be vaccinated has any illness with fever higher than 38.5°C; however, low-grade fever itself is not a reason to delay vaccination.
- If the person to be vaccinated is pregnant (in addition, pregnancy should be avoided for 1 month after vaccination, see **Pregnancy and breast-feeding**).

**Warnings and precaution**

If the person to be vaccinated has experienced any of the following, talk to the doctor or pharmacist before ProQuad is given:

- an allergic reaction to eggs or anything that contained egg.
- a history or family history of allergies or of convulsions (fits).
- a side effect after vaccination with measles, mumps, or rubella (in a single vaccine or combined vaccine, such as the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. or ProQuad) that involved easy bruising or bleeding for longer than usual.
- an infection with Human Immunodeficiency Virus (HIV) without showing symptoms of HIV disease. However, vaccination may be less effective than for uninfected persons (see **Do not use ProQuad**).

Once vaccinated, the person vaccinated should attempt to avoid for up to 6 weeks following vaccination, whenever possible, close association with the following individuals:

- Individuals with a lowered resistance to diseases.
- Pregnant women who have either not had chickenpox or have not been vaccinated against chickenpox.
- Newborn infants of mothers who have either not had chickenpox or have not been vaccinated against chickenpox.

Tell your doctor if there is anyone who falls into one of the categories above and is expected to be in contact with the person vaccinated after vaccination.

As with other vaccines, ProQuad may not completely protect all persons who are vaccinated. Also, if the person to be vaccinated has already been exposed to the measles, mumps, rubella, or varicella virus but is not yet ill, ProQuad may not be able to prevent the illness from appearing.

**Other medicines and ProQuad**

Tell your doctor or pharmacist if you or your child are taking or have recently taken any other medicines (or other vaccines).

ProQuad can be given at the same time as other childhood vaccines such as Prevenar, and/or hepatitis A vaccine, or with vaccines containing diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, or hepatitis B. A different place for the injection will be used for each vaccine.

The doctor may delay vaccination for at least 3 months following blood or plasma transfusions, or administration of immune globulin (IG), or varicella zoster immune globulin (VZIG). After vaccination with ProQuad, IG or VZIG should not be given for 1 month, unless your doctor tells you otherwise.

If a tuberculin test is to be performed, it should be done either any time before, simultaneously with, or 4 to 6 weeks after vaccination with ProQuad.

Tell the doctor if your child has recently received a vaccine or if one is scheduled to be given in the near future. The doctor will determine when ProQuad may be given.

The use of salicylates (for example, acetylsalicylic acid, a substance present in many medicines used to relieve pain and lower fever) should be avoided for 6 weeks following vaccination with ProQuad.

**Pregnancy and breast-feeding**

ProQuad should not be given to pregnant females. Females of child-bearing age should take the necessary precautions to avoid pregnancy for 1 month following vaccination.

Persons who are breast-feeding or who intend to breast-feed should tell the doctor. The doctor will decide if ProQuad should be given.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this vaccine.

**ProQuad contains sorbitol**

If you have been told by your doctor that you or your child has an intolerance to some sugars, inform your doctor before you or your child takes this vaccine.

## 3. How to use ProQuad

ProQuad should be injected under the skin in the upper arm or in the outer thigh.

ProQuad is not to be injected directly into any blood vessel.

ProQuad is given by injection as follows:

- Infants between 9 and 12 months of age:
  ProQuad may be administered from 9 months of age. To ensure optimal protection against chickenpox and measles, two doses of ProQuad should be given at least three months apart.
- Individuals 12 months of age and older:
  To ensure optimal protection against chickenpox, two doses of ProQuad should be given at least one month apart.

The appropriate time and number of injections will be determined by your doctor in accordance with official recommendations.

**Reconstitution instructions intended for medical and healthcare professionals are included at the end of the leaflet**

**If you forget to take ProQuad**

Your doctor will decide when to give the missed dose.

## 4. Possible side effects

Like all vaccines and medicines, this vaccine can cause side effects, although not everybody gets them.

The most common side effects reported with the use of ProQuad were: injection site complaints including pain/tenderness/soreness, redness, swelling or bruising; fever (38.9°C or higher);

irritability; rash (including measles-like rash, varicella-like rash, and injection-site rash); upper respiratory infection; vomiting and diarrhoea.

Other less common side effects have been reported following administration of ProQuad and some of these were serious. These included: allergic reactions (hives); seizures with a fever; cough and bronchiolitis (difficulty breathing with or without cough); and unsteadiness with walking.

Other side effects have been reported with the use of at least one of the following: ProQuad, previous formulations of monovalent and of the combined measles, mumps, and rubella vaccines manufactured by Merck & Co., Inc., or varicella vaccine live (Oka/Merck). These adverse events include: unusual bleeding or bruising under the skin, swelling of the testicles; tingling of the skin, herpes zoster (shingles); inflammation of the brain (encephalitis); severe skin disorders; skin infection; stroke; seizures without a fever; joint pain and/or swelling (which could be transient or chronic); and inflammation of the lung (pneumonia/pneumonitis); varicella (chickenpox).

The doctor has a more complete list of side effects for ProQuad and for the vaccine components for ProQuad (the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. and Varicella Vaccine live (Oka/Merck)).

If you or your child get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

## 5. How to store ProQuad

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the outer carton after EXP. The expiry dates refers to the last day of that month.

Store and transport refrigerated (2°C-8°C).

Keep the vial in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What ProQuad contains

After reconstitution, one dose (0.5 ml) contains:
The active substances are:

Measles virus[1] Enders' Edmonston strain (live, attenuated)..... not less than 3.00 $\log_{10}$ $CCID_{50}$*
Mumps virus[1] Jeryl Lynn™ (Level B) strain (live, attenuated)... not less than 4.30 $\log_{10}$ $CCID_{50}$*
Rubella virus[2] Wistar RA 27/3 strain (live, attenuated)..... not less than 3.00 $\log_{10}$ $CCID_{50}$*
Varicella virus[3] Oka/Merck strain (live, attenuated) ..... not less than 3.99 $\log_{10}$ PFU**

*50% cell culture infectious dose
**plaque-forming units

([1]) Produced in chick embryo cells.
([2]) Produced in human diploid lung (WI-38) fibroblasts.

([3]) Produced in human diploid cells (MRC-5).

The other ingredients are:

Powder
Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, hydrochloric acid and sodium hydroxide.

Solvent
Water for injections.

**What ProQuad looks like and contents of the pack**
The vaccine is a powder for suspension for injection contained in a single-dose vial, which should be mixed with solvent provided with the vial of powder.

ProQuad is available in pack of 1, 10 and 20. Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer Responsible for Batch Release: Merck Sharp and Dohme, B.V., Waarderweg, 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last revised in:**

**Other sources of information**

Detailed information on this medicine is available on the European Agency website: http://www.ema.europa.eu.

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**The following information is intended for healthcare professionals only:**

**Reconstitution instructions**

Before mixing with the solvent, the powder vaccine is a white to pale yellow compact crystalline cake. When completely mixed, the vaccine is a clear pale yellow to light pink liquid.

Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

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 use the reconstituted vaccine if you notice any particulate matter or if the appearance of the vaccine differs from that described above.

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

**See also section 3 How to use ProQuad.**