

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

ProQuad powder and solvent for suspension for injection

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 (approximately 0.5 mL) contains:

Measles virus<sup>1</sup> Enders' Edmonston strain (live, attenuated) ..... not less than 3.00 log<sub>10</sub> TCID<sub>50</sub> \*

Mumps virus<sup>1</sup> Jeryl Lynn (Level B) strain (live, attenuated) ..... not less than 4.30 log<sub>10</sub> TCID<sub>50</sub> \*

Rubella virus<sup>2</sup> Wistar RA 27/3 strain (live, attenuated) ..... not less than 3.00 log<sub>10</sub> TCID<sub>50</sub> \*

Varicella virus<sup>3</sup> Oka/Merck strain (live, attenuated) ..... not less than 3.99 log<sub>10</sub> PFU\*\*

\*50% tissue culture infectious dose

\*\*plaque-forming units

(<sup>1</sup>) Produced in chick embryo cells.

(<sup>2</sup>) Produced in human diploid lung (WI-38) fibroblasts.

(<sup>3</sup>) Produced in human diploid (MRC-5) cells.

The vaccine may contain traces of recombinant human albumin (rHA).

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

### Excipient(s) with known effect

The vaccine contains 16 milligrams of sorbitol per dose. See section 4.4.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection (powder 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 intramuscularly (IM) or subcutaneously (SC).

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

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

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

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

**The vaccine should under no circumstances be injected intravascularly.**

## 4.3 Contraindications

Hypersensitivity to any varicella vaccine or measles, mumps, or rubella vaccine or to any of the excipients listed in section 6.1, including neomycin (see sections 2 and 4.4).

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) (see section 4.8). 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 sections 4.4 and 4.8).

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 immunised 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**

##### Traceability

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

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).

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad as Reye 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-marketing experience suggests that transmission of varicella vaccine virus (Oka/Merck strain) resulting in varicella infection including disseminated disease may rarely occur between vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella including healthy as well as high-risk individuals (see section 4.8).

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

This vaccine should be given subcutaneously to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals.

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 Sharp & Dohme LLC, Rahway, NJ 07065, USA (herein after MSD), respectively.

#### Sodium

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

#### Potassium

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

#### Sorbitol

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

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 immunisation 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.

In a review of more than 3 500 susceptible women who were unknowingly in early stages of pregnancy when vaccinated with a rubella-containing vaccine, no cases of congenital rubella syndrome were reported. Post-marketing surveillance has identified congenital rubella syndrome associated with a rubella vaccine strain following inadvertent vaccination of a pregnant woman with a measles, mumps, and rubella vaccine.

Foetal damage has not been documented when measles, mumps or varicella vaccines have been given to pregnant women.

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 MSD and Varicella Vaccine live (Oka/Merck) were fever ( $\geq 39.4^{\circ}\text{C}$  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 MSD was rash at the injection site.

Following ProQuad given alone in 7 clinical trials, the observed rates of fever ( $\geq 39.4^{\circ}\text{C}$  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 ( $\geq 39.4^{\circ}\text{C}$  rectal equivalent) ranged from 15.2% to 27.2%.

In a clinical trial of ProQuad administered concomitantly with Infanrix Hexa, the rates of fever ( $\geq 38.0^{\circ}\text{C}$  rectal equivalent) were 69.3% following concomitant administration, 61.1% following ProQuad alone, and 57.3% following Infanrix Hexa alone; the rates of fever ( $\geq 39.4^{\circ}\text{C}$  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 intramuscularly

The general safety profiles of the IM and SC administration routes were comparable; however, fewer subjects experienced injection site adverse reactions in the IM group after each dose (see section 5.1 for study description).

#### 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 MSD

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 MSD (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 ( $\geq 39.4^{\circ}\text{C}$  rectal equivalent); irritability; rash (including measles-like rash, varicella-like rash, and injection site rash); upper respiratory infection; vomiting and diarrhoea.

#### b. Tabulated list 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 ( $\dagger$ ). Additionally, other adverse events 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 MSD, the monovalent component vaccines of the measles, mumps, and rubella vaccine manufactured by MSD, or Varicella Vaccine live (Oka/Merck). The frequency of these adverse events is qualified as "not known" when it cannot be estimated based on the available data.

Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$ ,  $< 1/10$ ); Uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); Rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); Not known (cannot be estimated from the available data)

| Adverse reactions                  | Frequency |
|------------------------------------|-----------|
| <b>Infections and infestations</b> |           |



|  |           |
|--|-----------|
| Adverse reactions  | Frequency |
| Ear infection, Gastroenteritis, Otitis media, Pharyngitis, Viral infection, Viral rash   | Uncommon  |
| Cellulitis, Respiratory tract infection, Skin infection, Tonsillitis, Varicella <sup>+</sup> ‡, Viral conjunctivitis   | Rare      |
| Aseptic meningitis*, Encephalitis*, Epididymitis, Herpes zoster*, Infection, Measles, Orchitis, Parotitis  | Not known |
| <b>Blood and lymphatic system disorders</b>  |           |
| Leukocytosis, Lymphadenopathy  | Rare      |
| Lymphadenitis, Thrombocytopenia  | Not known |
| <b>Immune system disorders</b>   |           |
| Hypersensitivity   | Rare      |
| Anaphylactoid reaction, Anaphylactic reaction, Angioedema, Face oedema, and Peripheral oedema  | Not known |
| <b>Metabolism and nutrition disorders</b>  |           |
| Decreased appetite   | Uncommon  |
| Dehydration  | Rare      |
| <b>Psychiatric disorders</b>   |           |
| Irritability   | Common    |
| Crying, Sleep disorder   | Uncommon  |
| Apathy, Clinging, Restlessness   | Rare      |
| <b>Nervous system disorders</b>  |           |
| Febrile seizure*, Somnolence   | Uncommon  |
| Ataxia, Seizure, Headache, Hyperkinesia, Hypersomnia, Lethargy, Tremor   | Rare      |
| Bell's palsy, Cerebrovascular accident, Dizziness, Encephalopathy*, Guillain-Barré syndrome, Measles inclusion body encephalitis (see section 4.3), Ocular palsies, Paraesthesia, Polyneuropathy, Subacute sclerosing panencephalitis*, Syncope, Transverse myelitis | Not known |
| <b>Eye disorders</b>   |           |
| Conjunctivitis, Eye discharge, Blepharitis, Eye irritation, Eye swelling, Ocular hyperaemia, Increased lacrimation, Ocular discomfort  | Rare      |
| Eyelid oedema, Optic neuritis, Retinitis, Retrobulbar neuritis   | Not known |
| <b>Ear and labyrinth disorders</b>   |           |
| Ear pain   | Rare      |
| Neurosensory deafness  | Not known |
| <b>Vascular disorders</b>  |           |
| Flushing, Pallor   | Rare      |
| Extravasation  | Not known |
| <b>Respiratory, thoracic, and mediastinal disorders</b>  |           |
| Cough, Respiratory tract congestion, Rhinorrhoea   | Uncommon  |
| Sinus disorder, Sneezing, Wheezing   | Rare      |
| Bronchospasm, Bronchitis, Pneumonitis (see section 4.3), Pneumonia, Rhinitis, Sinusitis, Oropharyngeal pain  | Not known |
| <b>Gastrointestinal disorders</b>  |           |
| Diarrhoea, Vomiting  | Common    |
| Abdominal pain upper, Nausea, Stomatitis   | Rare      |
| Abdominal pain, Haematochezia  | Not known |
| <b>Skin and subcutaneous tissue disorders</b>  |           |
| Measles-like rash‡, Rash, Varicella-like rash‡   | Common    |
| Dermatitis (including contact and atopic), Rubella-like rash‡, Urticaria, Erythema   | Uncommon  |
| Cold sweat, Exfoliative dermatitis, Drug eruption, Henoch-Schönlein purpura, Papular rash, Pruritus, Skin discolouration, Skin lesion, Zosteriform rash  | Rare      |

|  |             |
|--|-------------|
| Adverse reactions  | Frequency   |
| Erythema multiforme, Panniculitis, Purpura, Skin induration, Stevens-Johnson syndrome  | Not known   |
| <b>Musculoskeletal and connective tissue disorders</b>   |             |
| Arm pain, Musculoskeletal stiffness  | Rare        |
| Arthritis, Arthralgia*, Musculoskeletal pain, Myalgia, Swelling  | Not known   |
| <b>General disorders and administration site conditions</b>  |             |
| Fever <sup>‡</sup> , Erythema <sup>‡</sup> or Pain/Tenderness/Soreness <sup>‡</sup> at the injection site  | Very common |
| Ecchymosis or Swelling <sup>‡</sup> at the injection site, Injection site rash <sup>‡</sup>  | Common      |
| Asthenia, Fatigue, Injection site haemorrhage, Injection site induration, Injection site mass, Malaise   | Uncommon    |
| Influenza like illness, Injection site exfoliation, Injection site discolouration, Injection site pruritus, Injection site reaction, Injection site scar, Hyperthermia, Pain | Rare        |
| Injection site complaints (Pain, Oedema, Urticaria, Haematoma, Induration, Mass, Vesicles), Inflammation, Papillitis   | Not known   |
| <b>Investigations</b>  |             |
| Weight loss  | Rare        |
| <b>Injury, poisoning and procedural complications</b>  |             |
| Contusion  | Rare        |
| <b>Social circumstances</b>  |             |
| Activities of daily living impaired  | Rare        |

<sup>+</sup> Varicella caused by vaccine strain was observed in post-marketing use with Varicella Vaccine live (Oka/Merck).

<sup>‡</sup> Adverse events solicited in clinical trials.

\* 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.

#### Complications associated with varicella

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

#### 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 MSD, 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 MSD, 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

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 (see section 4.3); disseminated mumps and rubella vaccine virus infection has also been reported.

#### Subacute sclerosing panencephalitis

There is no evidence that measles vaccine can cause subacute sclerosing panencephalitis (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 unrecognised 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 post-marketing surveillance, the possibility exists that varicella vaccine virus (Oka/Merck strain) may rarely be transmitted to contacts of recipients of ProQuad who develop or do not develop a varicella-like rash (see section 4.4).

#### d. Other special populations

##### Immunocompromised individuals (see section 4.3)

Necrotising retinitis has been reported post-marketing in immunocompromised individuals.

##### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## 4.9 Overdose

Administration of a higher than recommended dose of ProQuad was reported rarely and the adverse reaction profile was comparable to that observed with the recommended dose of ProQuad.

## 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 MSD 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 MSD, 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 MSD.

More than 518 million doses of the measles, mumps, and rubella vaccine manufactured by MSD 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  $\geq 5$  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  $\geq 5$  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 randomised 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 MSD), 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 titre  $\geq 5$  gpELISA units/mL (an antibody titre 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 MSD 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<br>(seroprotection level)                            | Time point         | Dose 1 at 9 months /<br>Dose 2 at 12 months<br>N = 527 | Dose 1 at 11 months /<br>Dose 2 at 14 months<br>N = 480 | Dose 1 at 12 months /<br>Dose 2 at 15 months<br>N = 466 |
|--|--------------------|--|---|---|
|  |                    | Seroprotection rates<br>[95% CI]                       | Seroprotection rates<br>[95% CI]                        | Seroprotection rates<br>[95% CI]                        |
| <b>Measles</b><br>(titre $\geq 255$<br>mIU/mL)               | <b>Post-dose 1</b> | 72.3%<br>[68.2; 76.1]                                  | 87.6%<br>[84.2; 90.4]                                   | 90.6%<br>[87.6; 93.1]                                   |
|  | <b>Post-dose 2</b> | 94.6%<br>[92.3; 96.4]                                  | 98.1%<br>[96.4; 99.1]                                   | 98.9%<br>[97.5; 99.6]                                   |
| <b>Mumps</b><br>(titre $\geq 10$<br>ELISA Ab<br>units/mL)    | <b>Post-dose 1</b> | 96.4%<br>[94.4; 97.8]                                  | 98.7%<br>[97.3; 99.5]                                   | 98.5%<br>[96.9; 99.4]                                   |
|  | <b>Post-dose 2</b> | 99.2%<br>[98.0; 99.8]                                  | 99.6%<br>[98.5; 99.9]                                   | 99.3%<br>[98.1; 99.9]                                   |
| <b>Rubella</b><br>(titre $\geq 10$<br>IU/mL)                 | <b>Post-dose 1</b> | 97.3%<br>[95.5; 98.5]                                  | 98.7%<br>[97.3; 99.5]                                   | 97.8%<br>[96.0; 98.9]                                   |
|  | <b>Post-dose 2</b> | 99.4%<br>[98.3; 99.9]                                  | 99.4%<br>[98.1; 99.9]                                   | 99.6%<br>[98.4; 99.9]                                   |
| <b>Varicella</b><br>(titre $\geq 5$ gp<br>ELISA<br>units/mL) | <b>Post-dose 1</b> | 93.1%<br>[90.6; 95.1]                                  | 97.0%<br>[95.1; 98.4]                                   | 96.5%<br>[94.4; 98.0]                                   |
|  | <b>Post-dose 2</b> | 100%<br>[99.3; 100]                                    | 100%<br>[99.2; 100]                                     | 100%<br>[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 ( $\geq 5$  gpELISA Units/mL). The geometric mean titres (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 2 doses of ProQuad intramuscularly or subcutaneously

In a clinical trial, 405 children received 2 doses of ProQuad, either by the intramuscular or subcutaneous route of administration. Two doses of ProQuad administered by the IM route of administration were as immunogenic as two doses administered by the SC route in terms of antibody response rates and antibody titres to measles, mumps, rubella, and varicella.

#### 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 MSD

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 MSD 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 MSD 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 MSD 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 ( $\geq 5$  gpELISA Units/mL).

Experience with the measles, mumps, and rubella vaccine manufactured by MSD 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 hospitalisation 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 MSD, 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**

Not applicable.

### **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 Summary of Product Characteristics (SmPC).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Powder

Sucrose  
Hydrolysed gelatin  
Sodium chloride  
Sorbitol (E 420)  
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 (HCl) (to adjust pH)  
Sodium hydroxide (NaOH) (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, in-use stability has been demonstrated for 30 minutes when stored between 20°C and 25°C.

#### **6.4 Special precautions for storage**

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

Do not freeze.

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**

##### ProQuad with solvent for reconstitution supplied in a vial:

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

##### ProQuad with solvent for reconstitution supplied in a pre-filled syringe:

Powder in a vial (Type I glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe (Type I glass) with plunger stopper (bromo- or chlorobutyl rubber) and tip cap (styrene-butadiene rubber).

Pack sizes of 1, 10 and 20, either without needles, with 1 separate needle, or with 2 separate needles per pre-filled syringe.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

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

To reconstitute the vaccine, use only the solvent supplied, because it is free of preservatives or other antiviral substances, which might inactivate the vaccine.

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.

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

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

##### Reconstitution instructions

##### ProQuad with solvent for reconstitution supplied in a vial:

Withdraw the entire content of the solvent vial into a syringe. Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.



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

**Do not freeze the reconstituted vaccine.**

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

ProQuad with solvent for reconstitution supplied in a pre-filled syringe:

To attach the needle, it should be firmly placed on the tip of the syringe and secured by rotating.

Inject the entire content of the solvent syringe into the vial containing the powder. Gently agitate to dissolve completely.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

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

**Do not freeze the reconstituted vaccine.**

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

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

## **7. MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/323/001  
EU/1/05/323/002  
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: 06 April 2006

Date of latest renewal: 16 December 2015

#### **10. DATE OF REVISION OF THE TEXT**

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

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE  
SUBSTANCE(S) AND MANUFACTURER(S)  
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(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) of the biological active substance(s)

Merck Sharp & Dohme LLC  
770 Sumneytown Pike  
West Point, Pennsylvania  
19486 USA

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN 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 (PSURs)**

The requirements for submission of PSURs reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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 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, 1 dose (approximately 0.5 mL) contains (live, attenuated):

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

**3. LIST OF EXCIPIENTS**

Sucrose, hydrolysed gelatin, sodium chloride, E 420, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH, urea, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for suspension for injection  
1 vial (powder) + 1 vial (solvent)  
10 vials (powder) + 10 vials (solvent)

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

Intramuscular or 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. Do not freeze. 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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**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****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC  
SN  
NN



|   |
|---|
| <b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b><br><b>VIAL OF SOLVENT</b> |
|---|

|  |
|--|
| <b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b> |
|--|

Solvent for ProQuad

|                                    |
|------------------------------------|
| <b>2. METHOD OF ADMINISTRATION</b> |
|------------------------------------|

|                       |
|-----------------------|
| <b>3. EXPIRY DATE</b> |
|-----------------------|

EXP

|                        |
|------------------------|
| <b>4. BATCH NUMBER</b> |
|------------------------|

Lot

|  |
|--|
| <b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b> |
|--|

1 dose

|                 |
|-----------------|
| <b>6. OTHER</b> |
|-----------------|

MSD

**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, 1 dose (approximately 0.5 mL) contains (live, attenuated):

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

**3. LIST OF EXCIPIENTS**

Sucrose, hydrolysed gelatin, sodium chloride, E 420, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH, urea, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for suspension for injection

1 vial (powder) + 1 pre-filled syringe without needle (solvent)  
10 vials (powder) + 10 pre-filled syringes without needle (solvent)  
20 vials (powder) + 20 pre-filled syringes without needle (solvent)

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

Intramuscular or 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. Do not freeze. 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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**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****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

|  |
|--|
| <b>18. UNIQUE IDENTIFIER – HUMAN READABLE DATA</b> |
|--|

PC  
SN  
NN

**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, 1 dose (approximately 0.5 mL) contains (live, attenuated):

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

**3. LIST OF EXCIPIENTS**

Sucrose, hydrolysed gelatin, sodium chloride, E 420, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH, urea, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for suspension for injection

1 vial (powder) + 1 pre-filled syringe (solvent)+ 1 needle

10 vials (powder) + 10 pre-filled syringes (solvent)+ 10 needles

20 vials (powder) + 20 pre-filled syringes (solvent)+ 20 needles

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

Intramuscular or 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. Do not freeze. 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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**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****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

|  |
|--|
| <b>18. UNIQUE IDENTIFIER – HUMAN READABLE DATA</b> |
|--|

PC  
SN  
NN

**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, 1 dose (approximately 0.5 mL) contains (live, attenuated):

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

**3. LIST OF EXCIPIENTS**

Sucrose, hydrolysed gelatin, sodium chloride, E 420, monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, HCl, NaOH, urea, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for suspension for injection

1 vial (powder) + 1 pre-filled syringe (solvent)+ 2 needles

10 vials (powder) + 10 pre-filled syringes (solvent)+ 20 needles

20 vials (powder) + 20 pre-filled syringes (solvent)+ 40 needles

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

Intramuscular or 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. Do not freeze. 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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

**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****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

|  |
|--|
| <b>18. UNIQUE IDENTIFIER – HUMAN READABLE DATA</b> |
|--|

PC  
SN  
NN

|  |
|--|
| <b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b><br><b>VIAL OF POWDER</b> |
|--|

|  |
|--|
| <b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b> |
|--|

ProQuad powder for injection  
IM/SC

|                                    |
|------------------------------------|
| <b>2. METHOD OF ADMINISTRATION</b> |
|------------------------------------|

|                       |
|-----------------------|
| <b>3. EXPIRY DATE</b> |
|-----------------------|

EXP

|                        |
|------------------------|
| <b>4. BATCH NUMBER</b> |
|------------------------|

Lot

|  |
|--|
| <b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b> |
|--|

1 dose

|                 |
|-----------------|
| <b>6. OTHER</b> |
|-----------------|

MSD

|  |
|--|
| <b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b><br><b>SYRINGE OF SOLVENT</b> |
|--|

|  |
|--|
| <b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b> |
|--|

Solvent for ProQuad

|                                    |
|------------------------------------|
| <b>2. METHOD OF ADMINISTRATION</b> |
|------------------------------------|

|                       |
|-----------------------|
| <b>3. EXPIRY DATE</b> |
|-----------------------|

EXP

|                        |
|------------------------|
| <b>4. BATCH NUMBER</b> |
|------------------------|

Lot

|  |
|--|
| <b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b> |
|--|

1 dose

|                 |
|-----------------|
| <b>6. OTHER</b> |
|-----------------|

MSD

## **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. See section 4.

#### **What is in this leaflet**

1. What ProQuad is and what it is used for
2. What you need to know before you receive ProQuad
3. How to use ProQuad
4. Possible side effects
5. How to store ProQuad
6. Contents of the pack and other information

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

ProQuad is a vaccine containing measles, mumps, rubella, and chickenpox (varicella) 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 chickenpox (varicella). 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 chickenpox (varicella) 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 varicella vaccine or measles, mumps, or rubella vaccine or to any of the ingredients of this vaccine (listed in section 6) including neomycin.
- 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, and/or rubella-containing vaccines 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**).

If you have a blood clotting disorder or low levels of platelets in your blood, the injection will be given under the skin.

In rare circumstances, it is possible to catch chickenpox, including severe chickenpox, from a person who has been vaccinated with ProQuad. This may occur in persons who have not previously been vaccinated against chickenpox or have not had chickenpox, as well as persons who fall into one of the following categories:

- 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.

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

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 the person to be vaccinated is taking or has 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 the person to be vaccinated 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 women. Women 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 sodium**

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

### **ProQuad contains potassium**

This medicine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

### **ProQuad contains sorbitol**

This medicine contains 16 mg sorbitol per dose. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

## **3. How to use ProQuad**

ProQuad should be injected into the muscle or under the skin either in the area of the outer thigh or of the upper arm.

Usually for injections into the muscle the thigh area is preferred in young children, whereas for older individuals the upper arm area is the preferred injection site.

If the person to be vaccinated has a blood clotting disorder or low levels of platelets, the vaccine should be given under the skin because bleeding may occur following administration into the muscle.

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.

Allergic reactions (hives) may occur. Some of these reactions may be serious and may include difficulty in breathing or swallowing. If the vaccinated person has an allergic reaction, call your doctor right away.

Other side effects have been reported following administration of ProQuad and some of these were serious. These included:

- Uncommon (may affect up to 1 in 100 people): seizures with a fever.
- Rare (may affect up to 1 in 1,000 people): unsteadiness with walking.

The following other side effects reported with the use of ProQuad were:

- Very common (may affect more than 1 in 10 people): injection site complaints including pain/tenderness/soreness, redness, fever (38.9°C or higher);
- Common (may affect up to 1 in 10 people): injection site complaints including swelling or bruising; irritability; rash (including measles-like rash, varicella-like rash, and injection-site rash); upper respiratory infection; vomiting and diarrhoea.

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 Sharp & Dohme LLC, Rahway, NJ 07065, USA (herein after MSD), or Varicella Vaccine live (Oka/Merck). These adverse events include:

- Uncommon (may affect up to 1 in 100 people): cough.
- Rare (may affect up to 1 in 1,000 people): skin infection; chickenpox (varicella).
- Not known (frequency cannot be estimated from the available data): unusual bleeding or bruising under the skin, swelling of the testicles; tingling of the skin, herpes zoster (shingles); inflammation of the brain (encephalitis); inflammation of the coverings of the brain and spinal cord not caused by bacterial infection (aseptic meningitis), severe skin disorders; stroke; seizures without a fever; joint pain and/or swelling (which could be transient or chronic); and inflammation of the lung (pneumonia/pneumonitis).

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 MSD and Varicella Vaccine live (Oka/Merck)).

### **Reporting of side effects**

If the vaccinated person gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **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).

Do not freeze.

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 (approximately 0.5 mL) contains:

The active substances are:

Measles virus<sup>1</sup> Enders' Edmonston strain (live, attenuated) ..... not less than 3.00 log<sub>10</sub> TCID<sub>50</sub> \*

Mumps virus<sup>1</sup> Jeryl Lynn (Level B) strain (live, attenuated) ..... not less than 4.30 log<sub>10</sub> TCID<sub>50</sub> \*

Rubella virus<sup>2</sup> Wistar RA 27/3 strain (live, attenuated) ..... not less than 3.00 log<sub>10</sub> TCID<sub>50</sub> \*

Varicella virus<sup>3</sup> Oka/Merck strain (live, attenuated) ..... not less than 3.99 log<sub>10</sub> PFU\*\*

\*50% tissue culture infectious dose

\*\* plaque-forming units

(<sup>1</sup>) Produced in chick embryo cells.

(<sup>2</sup>) Produced in human diploid lung (WI-38) fibroblasts.

(<sup>3</sup>) Produced in human diploid cells (MRC-5).

The other ingredients are:

Powder

Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol (E 420), monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, hydrochloric acid (HCl) and sodium hydroxide (NaOH).

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.

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

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

### **Marketing Authorisation Holder and Manufacturer**

Merck Sharp & 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**

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UAB Merck Sharp & Dohme

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**Hrvatska**

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Limited  
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medinfoNI@msd.com

**This leaflet was last revised in**

**Other sources of information**

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

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

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

To reconstitute the vaccine, use only the solvent supplied, because it is free of preservatives or other antiviral substances, which might inactivate the vaccine.

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.

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

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

**Reconstitution instructions**

Withdraw the entire content of the solvent vial into a syringe. Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

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

**Do not freeze the reconstituted vaccine.**

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

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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What ProQuad is and what it is used for
2. What you need to know before you receive ProQuad
3. How to use ProQuad
4. Possible side effects
5. How to store ProQuad
6. Contents of the pack and other information

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

ProQuad is a vaccine containing measles, mumps, rubella, and chickenpox (varicella) 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 chickenpox (varicella). 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 chickenpox (varicella) 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 varicella vaccine or measles, mumps, or rubella vaccine or to any of the ingredients of this vaccine (listed in section 6) including neomycin.
- 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, and/or rubella-containing vaccines 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**).

If you have a blood clotting disorder or low levels of platelets in your blood, the injection will be given under the skin.

In rare circumstances, it is possible to catch chickenpox, including severe chickenpox, from a person who has been vaccinated with ProQuad. This may occur in persons who have not previously been vaccinated against chickenpox or have not had chickenpox, as well as persons who fall into one of the following categories:

- 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.

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

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 the person to be vaccinated is taking or has 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 the person to be vaccinated 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 women. Women 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 sodium**

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

### **ProQuad contains potassium**

This medicine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

### **ProQuad contains sorbitol**

This medicine contains 16 mg sorbitol per dose. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

## **3. How to use ProQuad**

ProQuad should be injected into the muscle or under the skin either in the area of the outer thigh or of the upper arm.

Usually for injections into the muscle the thigh area is preferred in young children, whereas for older individuals the upper arm area is the preferred injection site.

If the person to be vaccinated has a blood clotting disorder or low levels of platelets, the vaccine should be given under the skin because bleeding may occur following administration into the muscle.

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.

Allergic reactions (hives) may occur. Some of these reactions may be serious and may include difficulty in breathing or swallowing. If the vaccinated person has an allergic reaction, call your doctor right away.

Other side effects have been reported following administration of ProQuad and some of these were serious. These included:

- Uncommon (may affect up to 1 in 100 people): seizures with a fever.
- Rare (may affect up to 1 in 1,000 people): unsteadiness with walking.

The following other side effects reported with the use of ProQuad were:

- Very common (may affect more than 1 in 10 people): injection site complaints including pain/tenderness/soreness, redness; fever (38.9°C or higher);
- Common (may affect up to 1 in 10 people): injection site complaints including swelling or bruising; irritability; rash (including measles-like rash, varicella-like rash, and injection-site rash); upper respiratory infection; vomiting and diarrhoea.

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 Sharp & Dohme LLC, Rahway, NJ 07065, USA (herein after MSD), or Varicella Vaccine live (Oka/Merck). These adverse events include:

- Uncommon (may affect up to 1 in 100 people): cough.
- Rare (may affect up to 1 in 1,000 people): skin infection; chickenpox (varicella).
- Not known (frequency cannot be estimated from the available data): unusual bleeding or bruising under the skin, swelling of the testicles; tingling of the skin, herpes zoster (shingles); inflammation of the brain (encephalitis); inflammation of the coverings of the brain and spinal cord not caused by bacterial infection (aseptic meningitis), severe skin disorders; stroke; seizures without a fever; joint pain and/or swelling (which could be transient or chronic); and inflammation of the lung (pneumonia/pneumonitis).

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 MSD and Varicella Vaccine live (Oka/Merck)).

## **Reporting of side effects**

If the vaccinated person gets any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **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).

Do not freeze.

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 (approximately 0.5 mL) contains:

The active substances are:

Measles virus<sup>1</sup> Enders' Edmonston strain (live, attenuated) ..... not less than 3.00 log<sub>10</sub> TCID<sub>50</sub> \*

Mumps virus<sup>1</sup> Jeryl Lynn (Level B) strain (live, attenuated) ..... not less than 4.30 log<sub>10</sub> TCID<sub>50</sub> \*

Rubella virus<sup>2</sup> Wistar RA 27/3 strain (live, attenuated) ..... not less than 3.00 log<sub>10</sub> TCID<sub>50</sub> \*

Varicella virus<sup>3</sup> Oka/Merck strain (live, attenuated) ..... not less than 3.99 log<sub>10</sub> PFU\*\*

\*50% tissue culture infectious dose

\*\*plaque-forming units

(<sup>1</sup>) Produced in chick embryo cells.

(<sup>2</sup>) Produced in human diploid lung (WI-38) fibroblasts.

(<sup>3</sup>) Produced in human diploid cells (MRC-5).

The other ingredients are:

Powder

Sucrose, hydrolysed gelatin, urea, sodium chloride, sorbitol (E 420), monosodium glutamate, sodium phosphate, sodium bicarbonate, potassium phosphate, potassium chloride, medium 199 with Hanks' Salts, MEM, neomycin, phenol red, hydrochloric acid (HCl) and sodium hydroxide (NaOH).

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.

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

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

### Marketing Authorisation Holder and Manufacturer

Merck Sharp & 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:  
<https://www.ema.europa.eu>.

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

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

To reconstitute the vaccine, use only the solvent supplied, because it is free of preservatives or other antiviral substances, which might inactivate the vaccine.

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.

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

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

**Reconstitution instructions**

To attach the needle, it should be firmly placed on the tip of the syringe and secured by rotating.

Inject the entire content of the solvent syringe into the vial containing the powder. Gently agitate to dissolve completely.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.

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

**Do not freeze the reconstituted vaccine.**

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

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

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

#### **ANNEX IV**

#### **SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)**

**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for measles / mumps / rubella / varicella vaccines (live), the scientific conclusions of PRAC are as follows:

In view of available data on the literature regarding congenital rubella syndrome in pregnancy, the PRAC concluded that the product information of ProQuad (measles / mumps / rubella / varicella vaccines (live)) should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

**Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for measles / mumps / rubella / varicella vaccines (live) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing measles / mumps / rubella / varicella vaccines (live) is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.