SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:

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

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

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

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 in a pre-filled syringe.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ProQuad can be administered to individuals from 9 months of age under special circumstances: 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 to 12 years of age
  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 immunized with live measles virus vaccine. No studies have been reported to date on the effect of measles virus vaccines on children with untreated tuberculosis.

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

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

4.4 Special warnings and precautions for use

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 & Co., Inc., 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 immunization with ProQuad.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnant women should not be vaccinated with ProQuad.

Studies have not been conducted with ProQuad in pregnant women. It is not known whether ProQuad can cause foetal harm when administered to a pregnant woman or affect reproduction capacity.

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

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

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

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

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

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

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

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

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

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

b. Tabulated 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 (‡). 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 Merck & Co., Inc., the monovalent component vaccines of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., or Varicella Vaccine live (Oka/Merck). The frequency of these adverse events is qualified as "not known" when it cannot be estimated based on the available data.

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

Adverse reactions	Frequency
Infections and infestations	
Ear infection, Gastroenteritis, Otitis media, Pharyngitis, Viral infection, Viral rash	Uncommon
Cellulitis, Respiratory tract infection, Skin infection, Tonsillitis, Varicella+ ‡, Viral conjunctivitis	Rare
Aseptic meningitis*, Encephalitis*, Epididymitis, Herpes zoster*, Infection, Measles, Orchitis, Parotitis	Not known
Blood and lymphatic system disorders	
Leukocytosis, Lymphadenopathy	Rare
Lymphadenitis, Thrombocytopenia	Not known
Immune system disorders	
Hypersensitivity	Rare
Anaphylactoid reaction, Anaphylactic reaction, Angioedema, Face oedema, and Peripheral oedema	Not known
Metabolism and nutrition disorders	
Decreased appetite	Uncommon
Dehydration	Rare
Psychiatric disorders	
Irritability	Common
Crying, Sleep disorder	Uncommon

Apathy, Clinging, Restlessness	Rare
Nervous system disorders	
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
Eye disorders	
Conjunctivitis, Eye discharge, Blepharitis, Eye irritation, Eye swelling, Ocular hyperaemia, Increased lacrimation, Ocular discomfort	Rare
Eyelid oedema, Optic neuritis, Retinitis, Retrobulbar neuritis	Not known
Ear and labyrinth disorders	
Ear pain	Rare
Neurosensory deafness	Not known
Vascular disorders	
Flushing, Pallor	Rare
Extravasation	Not known
Respiratory, thoracic, and mediastinal disorders	
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
Gastrointestinal disorders	
Diarrhoea, Vomiting	Common
Abdominal pain upper, Nausea, Stomatitis	Rare
Abdominal pain, Haematochezia	Not known
Skin and subcutaneous tissue disorders	
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
Erythema multiforme, Panniculitis, Purpura, Skin induration, Stevens-Johnson syndrome	Not known
Musculoskeletal and connective tissue disorders	
Arm pain, Musculoskeletal stiffness	Rare
Arthritis, Arthralgia*, Musculoskeletal pain, Myalgia, Swelling	Not known
General disorders and administration site conditions	
Fever‡, Erythema‡ or Pain/Tenderness/Soreness‡ at the injection site	Very common

Ecchymosis or Swelling‡ at the injection site, Injection site rash‡	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
Investigations	
Weight loss	Rare
Injury, poisoning and procedural complications	
Contusion	Rare
Social circumstances	
Activities of daily living impaired	Rare

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

c. Description of selected adverse reactions

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

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 or 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 Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck) (N=31,298). These data suggest one additional case of febrile seizure per 2600 children vaccinated with ProQuad compared with separate administration of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck). These data were confirmed by a post-marketing observational study sponsored by the U.S. Centers for Disease Control and Prevention.
In the 30-day timeframe following vaccination, no increased risk of febrile seizures was observed (see section 5.1).

Encephalitis and encephalopathy
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.

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

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

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

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

Active surveillance data in children vaccinated with Varicella Vaccine live (Oka/Merck) and followed for 14 years after vaccination showed no increase in the frequency of herpes zoster compared to children with prior wild-type varicella during the pre-vaccine era. These surveillance data actually suggest that varicella-vaccinated children may have a lower risk of herpes zoster. However, the long term effect of varicella vaccination on the incidence of herpes zoster is unknown at present. There are no long-term data currently available with ProQuad (see section 5.1).

Transmission
Based on 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)
Necrotizing 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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 Merck & Co., Inc. has been demonstrated in numerous studies.

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

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

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

In a study comparing 1 dose (N=1114) to 2 doses (N=1102) of Varicella Vaccine live (Oka/Merck), the estimated vaccine efficacy against all severities of varicella disease for the 10-year observation period was 94% for 1 dose and 98% for 2 doses ($p<0.001$). Over the 10-year observation period, the cumulative rate of varicella was 7.5% after 1 dose and 2.2% after 2 doses. Most cases of varicella reported in recipients of 1 dose or 2 doses of vaccine were mild.

Antibody responses against varicella virus ≥5 gpELISA Units/mL in the glycoprotein enzyme-linked immunosorbent assay (gpELISA, a highly sensitive assay which is not commercially available) have been shown to be highly correlated with long-term protection. Clinical studies have shown that immunization

with ProQuad elicits rates of antibody responses against varicella virus ≥5 gpELISA Units/mL similar to those observed after vaccination with Varicella Vaccine live (Oka/Merck).

Immunogenicity

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

Clinical trials involving 6987 subjects who received ProQuad demonstrated detectable immune responses to measles, mumps, rubella, and varicella in a high proportion of individuals. The presence of detectable antibody was assessed by an appropriately sensitive enzyme-linked immunosorbent assay (ELISA) for measles, mumps (wild-type and vaccine-type strains), and rubella, and by gpELISA for varicella. Following a single dose of ProQuad, the vaccine response rates were 97.7% for measles, 96.3% to 98.8% for mumps, and 98.8% for rubella. While the seroconversion rate for varicella was uniformly high (97.9% to 99.8% across all studies), seroconversion has not been shown to correlate well with protection. The vaccine response rate was 90.9% (range 80.8% to 94.5%) for varicella based on a post-vaccination antibody titre ≥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 Merck & Co., Inc. at separate injection sites.

Evaluation of immunogenicity in children from 9 to 12 months of age at the time of first dose

A clinical study was conducted with ProQuad administered with a 2-dose schedule, the doses being given 3 months apart in 1,620 healthy subjects from 9 to 12 months of age at the time of first dose. The safety profile post-dose 1 and 2 was generally comparable for all age cohorts.

In the Full Analysis Set (vaccinated subjects regardless of their antibody titre at baseline), high seroprotection rates of >99% were elicited to mumps, rubella, and varicella post-dose 2, regardless of the age of the vaccinees at the first dose. After 2 doses, the seroprotection rates against measles were 98.1% when the first dose was given at 11 months, compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective met). After two doses, the seroprotection rates against measles were 94.6% when the first dose was given at 9 months, compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective not met).

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

Valence (seroprotection level)	**Time point**	**Dose 1 at 9 months / Dose 2 at 12 months N = 527**	**Dose 1 at 11 months / Dose 2 at 14 months N = 480**	**Dose 1 at 12 months / Dose 2 at 15 months N = 466**
		Seroprotection rates [95% CI]	**Seroprotection rates [95% CI]**	**Seroprotection rates [95% CI]**
	Post-dose 1	72.3% [68.2; 76.1]	87.6% [84.2; 90.4]	90.6% [87.6; 93.1]

Measles (titre ≥255 mIU/mL)	**Post-dose 2**	94.6% [92.3; 96.4]	98.1% [96.4; 99.1]	98.9% [97.5; 99.6]
Mumps (titre ≥10 ELISA Ab units/mL)	**Post-dose 1**	96.4% [94.4; 97.8]	98.7% [97.3; 99.5]	98.5% [96.9; 99.4]
	Post-dose 2	99.2% [98.0; 99.8]	99.6% [98.5; 99.9]	99.3% [98.1; 99.9]
Rubella (titre ≥10 IU/mL)	**Post-dose 1**	97.3% [95.5; 98.5]	98.7% [97.3; 99.5]	97.8% [96.0; 98.9]
	Post-dose 2	99.4% [98.3; 99.9]	99.4% [98.1; 99.9]	99.6% [98.4; 99.9]
Varicella (titre ≥5 gp ELISA units/mL)	**Post-dose 1**	93.1% [90.6; 95.1]	97.0% [95.1; 98.4]	96.5% [94.4; 98.0]
	Post-dose 2	100% [99.3; 100]	100% [99.2; 100]	100% [99.2; 100]

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

Children who received a second dose of ProQuad

In 2 clinical trials, 1035 subjects were administered a second dose of ProQuad approximately 3 months after the first dose. The vaccine response rates were 99.4% for measles, 99.9% for mumps, 98.3% for rubella, and 99.4% for varicella (≥5 gpELISA Units/mL). The geometric mean 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 Merck & Co., Inc.

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

Persistence of immune response

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2108 subjects who were involved in 1 clinical trial. The antibody persistence rates 1 year postvaccination in recipients of a

single dose of ProQuad were 98.9% (1722/1741) for measles, 96.7% (1676/1733) for mumps, 99.6% (1796/1804) for rubella, and 97.5% (1512/1550) for varicella (≥5 gpELISA Units/mL).

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

Observational studies of long-term effectiveness of varicella vaccine
Surveillance data from two U.S. observational effectiveness studies confirmed that widespread varicella vaccination reduces the risk of varicella by approximately 90% and that protection is maintained over at least 15 years both in vaccinated and unvaccinated individuals. These data also suggest that varicella vaccination may reduce the risk of herpes zoster in vaccinated individuals.

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

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

Post-marketing observational safety surveillance study
Safety was evaluated in an observational study that included 69,237 children vaccinated with ProQuad 12 months to 12 years old and 69,237 matched children in a historical comparison group who were vaccinated concomitantly with the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., and the Varicella Vaccine live (Oka/Merck). In addition to assessing the incidence of febrile seizures occurring within 30 days after the first dose (see section 4.8), the study also assessed the general safety of ProQuad in the 30-day period after the first or second dose. Other than the increase in febrile seizure after the first dose, no safety concerns after the first or second dose were identified.

5.2 Pharmacokinetic properties

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
Sorbitol
Gelatin *(hydrolyzed porcine)*
Urea
Sodium chloride
Sodium phosphate
Medium 199 with Hanks' Salts
Monosodium L glutamate Monohydrate
Minimum Essential Medium, Eagle
Sodium bicarbonate
Potassium phosphate
Potassium chloride
Neomycin
Phenol red
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

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

The expiry date of the product is indicated on the packaging materials.

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

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 (chlorobutyl rubber) and tip cap (styrene-butadiene rubber), without needle, in a pack size of 1 and 10.

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 (chlorobutyl rubber) and tip cap (styrene-butadiene rubber), with one or two unattached needles, in a pack size of 1 and 10.

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

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

Inject the entire content of the 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. REGISTRATION HOLDER AND IMPORTER

Merck Sharp & Dohme (Israel – 1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon, Israel

8. MARKETING AUTHORISATION NUMBER

154-72-34392

Revised in January 2024 according to the MOH guidelines.