AUSTRALIAN PRODUCT INFORMATION – PROQUAD® Measles, Mumps, Rubella and Varicella Virus Vaccine Live (Refrigerator stable formulation)

1 NAME OF THE MEDICINE

Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live

2 QUALITATIVE AND QUANTITATIVE COMPOSITION and 3 PHARMACEUTICAL FORM

ProQuad is a sterile lyophilised preparation of (1) the components of M-M-R® II (Measles, Mumps and Rubella Virus Vaccine Live): a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; the Jeryl Lynn (B level) strain of mumps virus propagated in chick embryo cell culture; the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts; and (2) the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells (same varicella strain as in VARIVAX).

ProQuad, when reconstituted as directed, is a sterile preparation for intramuscular (IM) or subcutaneous (SC) administration. Each approximately 0.5 mL dose contains not less than 3.00 $\log_{10}$ $TCID_{50}$ (50% tissue culture infectious dose) of measles virus; 4.30 $\log_{10}$ $TCID_{50}$ of mumps virus; 3.00 $\log_{10}$ $TCID_{50}$ of rubella virus; and a minimum of 3.99 log10 PFU (plaque-forming units) of Oka/Merck varicella virus.

Powder for injection.

Before reconstitution, the lyophilised vaccine is a white to pale yellow compact crystalline powder. ProQuad, when reconstituted, is a clear pale yellow to light pink liquid.

Excipients with known effect: The vaccine contains 16 mg of sorbitol.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

This product also contains residual components of MRC-5 cells including DNA and protein, recombinant human albumin, bovine serum albumin and other buffer and media ingredients.

This product contains no preservative.

The cells, virus pools, bovine serum, and recombinant human albumin used in manufacturing are all screened to ensure the absence of adventitious agents.

The manufacture of this product includes exposure to bovine derived material. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Individuals aged 12 months to 12 years should receive a single dose of ProQuad administered subcutaneously or intramuscularly.

If the first dose of a measles-containing vaccine is given between 6 months of age and less than 12 months of age (in an at-risk situation such as measles outbreak, or due to official recommendations) the response to the vaccine may be adversely influenced by circulating maternal antibodies. Therefore, another dose of a measles-containing vaccine should be given at 12 months of age or later. A subsequent (third) dose can be administered if warranted by official recommendations for a measles-containing vaccine.

At least one month should elapse between a dose of M-M-R II and ProQuad. If a second dose of varicella-containing vaccine is administered, there should be a minimum interval of 1 month between doses.

Do not give immune globulin (Ig) or Varicella-Zoster Immune Globulin (VZIG) concomitantly with ProQuad (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Method of administration

FOR SUBCUTANEOUS OR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVASCULARLY.

The vaccine is to be injected in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

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

CAUTION: A sterile syringe free of preservatives, antiseptics, detergents, and other antiviral substances must be used for each injection and/or reconstitution of ProQuad because these substances may inactivate the vaccine viruses.

To reconstitute the vaccine, use only the diluent supplied because it is free of preservatives or other antiviral substances, which might inactivate the vaccine viruses. The diluent may be supplied in a separate carton.

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

The vials are for single use in one patient only.

Withdraw the entire volume of solvent into a syringe (if a prefilled syringe is available, this step is not necessary). Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 60 MINUTES (1 HOUR) WHEN STORED AT 20ºC to 25°C

OR WITHIN 150 MINUTES (2.5 HOURS) WHEN STORED AT 2ºC to 8°C.

4.3 CONTRAINDICATIONS

❖ History of hypersensitivity to any component of the vaccine, including gelatin.

❖ History of anaphylactoid reaction to neomycin.

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

❖ Immunosuppressive therapy (including high-dose corticosteroids); however, ProQuad is not contraindicated for use in individuals who are receiving topical corticosteroids or low-dose corticosteroids, as are commonly used for asthma prophylaxis or in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease. Vaccination with a live attenuated vaccine, such as varicella, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals.

❖ Primary and acquired immunodeficiency states, including immunosuppression in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinaemic and dysgammaglobulinaemic states. Measles inclusion body encephalitis, pneumonitis, and death as a direct consequence of disseminated measles vaccine virus infection have been reported in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

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

❖ Active untreated tuberculosis.

❖ Any active febrile illness with fever >38.5°C (>101.3°F); however, low-grade fever itself is not a contraindication to vaccination.

❖ Do not give ProQuad to pregnant females. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. (See Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy.)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Due caution should be employed in administration of ProQuad to persons with individual or family history of convulsions, a history of cerebral injury or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation that may occur following vaccination (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

The safety and efficacy of ProQuad have not been established in individuals who are known to be infected with human immunodeficiency viruses with or without evidence of immunosuppression (see Section 4.3 CONTRAINDICATIONS).

The duration of protection from measles, mumps, rubella, and varicella infection after vaccination with ProQuad is unknown (see Section 5 PHARMACOLOGICAL PROPERTIES).

As for any vaccine, 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 (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in lactation).

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

Post-licensing experience suggests that transmission of varicella vaccine virus (Oka/Merck) resulting in varicella infection including disseminated disease may occur rarely between vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella including healthy as well as high-risk individuals.

High-risk individuals susceptible to varicella include:
- Immunocompromised individuals (see Section 4.3 CONTRAINDICATIONS),
- 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.

Hypersensitivity to Eggs
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 after receiving vaccines containing traces of chick embryo antigen. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur.

Thrombocytopenia and Coagulation disorders
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.

No clinical data are available 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; with measles, mumps, and rubella vaccine; and with 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 potential risk-to-benefit ratio should be carefully evaluated before considering vaccination with ProQuad in such cases (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Post-Exposure Prophylaxis
No clinical data are available for ProQuad Frozen administered after exposure to measles, mumps, rubella or varicella; however, post-exposure prophylaxis has been demonstrated for measles and varicella with measles-containing vaccine and varicella virus vaccine, respectively. Vaccination of susceptible individuals within 3 days of exposure to wild-type measles may provide some protection. Vaccination of susceptible individuals within 3 days of exposure to wild type varicella may prevent a clinically apparent infection or modify the course of the infection. In addition, there are limited data that indicate that vaccination up to 5 days after exposure to varicella may modify the course of the infection.

Adolescents and Adults
No clinical data are available on the safety, immunogenicity, and efficacy of ProQuad in adolescents and adults.

Tuberculin Test
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 ProQuad.

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

Use in the elderly
No data available.

Paediatric use
ProQuad has not been studied in infants less than 12 months of age and is not recommended for administration in this age group.

Effects on laboratory tests
See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Tuberculin Test.*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Administration of immune globulins (Ig) 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 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).

Following administration of ProQuad, any Ig including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination.

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.

Concomitant use with other vaccines
At least 1 month should elapse between a dose of M-M-R II and a dose of ProQuad. If for any reason a second dose of varicella-containing vaccine is required, at least 1 month should elapse between administration of the 2 doses.

The fourth dose of DTaP (diphtheria, tetanus, acellular pertussis vaccine) is indicated for children 15 months of age and older. Limited data suggest that ProQuad may be administered concomitantly (at separate injection sites) with DTaP in children 15 months of age and older (for children less than 15 months of age see Section 5 PHARMACOLOGICAL PROPERTIES).

Results from clinical studies indicate that ProQuad may be administered concomitantly with *Haemophilus* b conjugate (meningococcal protein conjugate), hepatitis B (recombinant), *Pneumococcal 7-valent Conjugate and/or Hepatitis A vaccines* for children 12 to 15 months of age.

There are no data for the administration of ProQuad with inactivated poliovirus vaccine.

There are no data for concurrent administration of ProQuad and DTaP containing vaccines registered in Australia (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Studies with Other Vaccines).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Impairment of fertility
ProQuad has not been evaluated for its potential to impair fertility.

Females of Childbearing Age
In females of childbearing age, pregnancy should be avoided for 3 months following vaccination (see Use in pregnancy).

Use in pregnancy *(Category B2)*
Studies have not been conducted with ProQuad in pregnant women. ProQuad should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see Sections 4.1 THERAPEUTIC INDICATIONS and 4.3 CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) Reports have indicated that contracting wild-type measles during pregnancy enhances foetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to wild-type measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse foetal effects; (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and foetus, there is no evidence that it causes congenital malformations in humans; (3) Wild-type rubella infection during pregnancy, especially in the first trimester, can lead to miscarriage, stillbirth, or Congenital Rubella Syndrome (CRS). In an 18-year survey involving over 1200 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 683 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with

CRS. Subsequent post-marketing surveillance has identified CRS associated with a rubella vaccine strain following inadvertent vaccination of a pregnant female with a measles, mumps, and rubella vaccine; and (4) Wild-type varicella can sometimes cause harm to the foetus.

In the first 10 years of the Pregnancy Registry for varicella vaccine (Oka/Merck), of 139 seronegative women and 449 women of unknown serostatus who received varicella vaccine during pregnancy or within 3 months before pregnancy, none had newborns with abnormalities compatible with congenital varicella syndrome.

Use in lactation
It is not known whether measles, mumps, or varicella virus is secreted in human milk. Studies have shown that lactating 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 who developed serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Therefore, caution should be exercised when ProQuad is administered to a nursing woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Children 12 through 23 months of age
In clinical trials, ProQuad was administered subcutaneously to 6038 children 12 through 23 months of age without concomitant administration. ProQuad was generally well tolerated.

Children received either the refrigerator-stable formulation or the frozen formulation of ProQuad and were monitored for 6 weeks post vaccination. The safety profiles were similar for the two formulations. The safety of the frozen formulation of ProQuad was compared with the safety of M-M-R II and VARIVAX given concomitantly at separate injection sites. The safety profile for ProQuad was similar to the component vaccines.

The only systemic vaccine-related adverse experiences that were reported at a significantly greater rate in individuals who received ProQuad than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites were fever (≥38.9°C [≥102°F] oral equivalent or abnormal) (21.5% versus 14.9%, respectively), and measles-like rash (3.0% versus 2.1%, respectively). 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 than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites (22.0% versus 26.7%, respectively). The only vaccine-related injection site adverse experience that was more frequent among recipients of ProQuad than recipients of M-M-R II and VARIVAX was rash at the injection site (2.3% versus 1.5%, respectively).

Across clinical studies, the following adverse experiences were reported as vaccine-related by the investigator in individuals after a single dose of ProQuad (excluding single events with a frequency ≤0.02%). Several adverse experiences were solicited in the clinical studies and are designated with the symbol (†).

[Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000)]

Infections and infestations
Common: upper respiratory infection
Uncommon: gastroenteritis, ear infection/otitis, nasopharyngitis, otitis media, pharyngitis, viral infection, viral rash
Rare: tonsillitis, varicella†, viral gastroenteritis

Blood and lymphatic disorders
Rare: lymphadenopathy

Immune system disorders
Rare: allergy/hypersensitivity

Metabolism and nutrition disorders
Uncommon: anorexia, decreased appetite

Psychiatric disorders
Common: irritability
Uncommon: crying, insomnia, sleep disorder
Rare: agitation, clinging

Nervous system disorders
Uncommon: febrile seizure (see below), somnolence
Rare: ataxia, headache, lethargy

Eye disorders
Rare: conjunctivitis, tearing, visual discomfort

Ear and labyrinth disorders
Rare: ear pain

Vascular disorders
Rare: flushing

Respiratory, thoracic, and mediastinal disorders
Uncommon: cough, nasal congestion, respiratory congestion, rhinorrhoea
Rare: wheezing

Gastrointestinal disorders
Common: diarrhoea, vomiting
Rare: nausea

Skin and subcutaneous tissue disorders
Common: measles-like rash†, rash, varicella-like rash†
Uncommon: dermatitis (including contact and atopic), erythema, rubella-like rash†, urticaria, viral exanthema
Rare: drug eruption, exanthema

General disorders and administration site conditions
Very common: fever ≥38.9°C ([≥102°F] oral equivalent or abnormal)†, erythema† or pain/tenderness/soreness† at the injection site
Common: ecchymosis or swelling† at the injection site, injection site rash†
Uncommon: asthenia/fatigue, induration or warmth at the injection site, injection site haemorrhage, injection site mass/lump, malaise
Rare: flu-like/influenza-like illness, injection site discoloration, injection site reaction, pain, pain/tenderness/soreness

Injury and poisoning, and procedural complications
Rare: contusion

Other Adverse Experiences
Additionally, adverse experiences reported with post-marketing use of ProQuad and/or in clinical studies and/or post-marketing use of M-M-R II, the component vaccines, and VARIVAX without regard to causality or frequency are summarized below.

Infections and infestations
atypical measles, cellulitis, epididymitis, herpes zoster‡, infection, measles, orchitis, parotitis, respiratory infection, skin infection, varicella (vaccine strain)

Blood and the lymphatic system disorders
aplastic anaemia, lymphadenitis, regional lymphadenopathy, thrombocytopenia including immune thrombocytopenia (ITP)

Immune system disorders
anaphylactoid reaction, anaphylaxis and related phenomenon such as angioneurotic oedema, facial oedema, and peripheral oedema, anaphylaxis in individuals with or without an allergic history

Psychiatric disorders
apathy

Nervous system disorders
acute disseminated encephalomyelitis (ADEM), afebrile convulsions or seizures, aseptic meningitis (see below), Bell's palsy, cerebrovascular accident, dizziness, encephalitis‡ (see below), encephalopathy (see below), Guillain-Barré syndrome, hypersomnia, measles inclusion body encephalitis (see Section 4.3 CONTRAINDICATIONS), meningitis‡, ocular palsies, paraesthesia, polyneuritis, polyneuropathy, subacute sclerosing panencephalitis (see below), syncope, transverse myelitis, tremor

‡Cases caused by wild-type varicella or vaccine strain varicella have been reported in immunocompromised and immunocompetent individuals administered VARIVAX (same varicella vaccine strain as in ProQuad).

Eye disorders
oedema of the eyelid, irritation, necrotising retinitis (reported only in immunocompromised individuals), optic neuritis, retinitis, retrobulbar neuritis

Ear and labyrinth disorders
nerve deafness

Vascular disorders
extravasation

Respiratory, thoracic and mediastinal disorders
bronchial spasm, bronchitis, pneumonitis (see Section 4.3 CONTRAINDICATIONS), pneumonia, pulmonary congestion, rhinitis, sinusitis, sneezing, sore throat

Gastrointestinal disorders
abdominal pain, haematochezia, mouth ulcer

Skin and subcutaneous tissue disorders

erythema multiforme, Henoch-Schőnlein purpura, panniculitis, pruritus, purpura, skin induration, Stevens-Johnson syndrome, acute haemorrhagic oedema of infancy, skin granuloma associated with vaccine derived rubella virus

Musculoskeletal, connective tissue and bone disorders
arthritis and/or arthralgia (usually transient and rarely chronic [see below]), musculoskeletal pain, myalgia, swelling

General disorders and administration site conditions
injection site complaints (burning and/or stinging of short duration, oedema/swelling, hive-like rash, haematoma, induration, lump, vesicles, wheal and flare), inflammation, papillitis, stiffness, varicella-like rash, warm sensation, warm to touch

Children who received ProQuad intramuscularly
The general safety profiles of the IM and SC administration routes were comparable.

Post-marketing safety surveillance
Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals (see Section 4.3 CONTRAINDICATIONS). No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of the combination of measles, mumps, and rubella vaccine contained in M-M-R II. Since 1978, post-marketing surveillance of M-M-R II indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (1 per 1000 reported cases).

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 CONTRAINDICATIONS); disseminated mumps and rubella vaccine virus infection have also been reported.

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 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.

There have been reports of subacute sclerosing panencephalitis (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. Based on estimated measles vaccine distribution in the United States (US), the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6 to 22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the US Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

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.

Children who received ProQuad intramuscularly
In a clinical trial, 405 children received ProQuad either intramuscularly (n=202) or subcutaneously (n=203). The general safety profiles of the intramuscular and subcutaneous administration routes were comparable; however, fewer subjects experienced injection-site adverse reactions in the intramuscular group.

Febrile seizures have been reported in children receiving ProQuad. A post-marketing observational study was conducted in 31,298 children 12 to 60 months of age who received their first dose of ProQuad, 99% of whom were in their second year of life. These children had not received prior MMR and varicella vaccinations and had not had measles, mumps, rubella, or varicella wild-type infections. In this population, the incidence of febrile seizures 5 to 12 days after vaccination with the first dose of ProQuad was 0.7 per 1000 children (n=22). This incidence was two-fold higher than the incidence (0.3 per 1000 children, n=10) observed in children from a historical, age- and gender-matched control group (N=31,298) vaccinated concomitantly with M-M-R II and VARIVAX. The febrile seizures relative risk (RR) was 2.20 (95% confidence interval: 1.04, 4.65). In the 0 to 30 day time period following vaccination, the incidence of febrile seizures with ProQuad (1.4 per 1000 children, n=44) was not greater than that observed in children receiving M-M-R II and VARIVAX concomitantly (1.3 per 1000 children, n=40).

In the 3 post-licensure clinical trials evaluating the concomitant use of ProQuad with other paediatric vaccines, a total of 1745 children 12 to 23 months of age received 2 doses of ProQuad, of which 1661 completed safety follow-up after both doses. Rates of adverse experiences after the second dose of ProQuad were generally similar to, or lower than, those seen with the first dose. The fever rate was lower after the second dose than after the first dose.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ProQuad is a combined attenuated live virus vaccine containing measles, mumps, rubella, and varicella viruses.

Measles, mumps, rubella, and varicella are 4 common childhood diseases caused by measles virus, mumps virus, rubella virus, and varicella virus, respectively. These diseases may be associated with serious complications and/or death. For example, measles can be associated with pneumonia and encephalitis; mumps can be associated with aseptic meningitis, deafness, and orchitis; rubella occurring during pregnancy can cause congenital rubella syndrome in the infants of infected mothers; and wild-type varicella can be associated with bacterial superinfection, pneumonia, encephalitis, and Reye syndrome.

Clinical trials

Efficacy
Formal studies to evaluate the efficacy of ProQuad have not been performed. However, the efficacy of M-M-R II and VARIVAX 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 produced by Merck Sharp & Dohme LLC, Rahway, NJ 07065, USA 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 M-M-R II.

More than 518 million doses of M-M-R II 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. Vaccination against measles, mumps, and rubella has led to a significant reduction in the incidence of these diseases.

In combined clinical trials of VARIVAX, the protective efficacy of the vaccine against all forms of varicella 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. Long-term estimated efficacy for the vaccine against all forms of varicella over 10 years was 94%. Antibody responses against varicella virus ≥5 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 vaccination with ProQuad elicits rates of antibody responses against varicella virus ≥5 units/mL in the gpELISA similar to those observed after vaccination with VARIVAX.

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 in a single study. In this study, 1006 subjects were vaccinated with the refrigerator-stable formulation and 513 were vaccinated with the frozen formulation. Four clinical trials had previously established that the earlier formulation of ProQuad was similar to the individual component vaccines (M-M-R II and VARIVAX), which

are currently used in routine vaccination in some countries.

Thus, there were a total of 5 clinical trials involving 6987 subjects who received either the refrigerator stable formulation of ProQuad or the frozen formulation of ProQuad. These clinical trials 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. The vaccine response rate was 90.9% for varicella based on an antibody response rate ≥5 gpELISA units/mL (a response rate 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 M-M-R II and VARIVAX at separate injection sites (see Table 1).

Table 1
Summary of Combined Immunogenicity Results 6 weeks Following the Administration of a Primary Dose of ProQuad (Varicella Virus Potency ≥ 3.97 $\log_{10}$ PFU) or M-M-R II and VARIVAX (Per-Protocol-Population)

Group	Antigen	n	Observed Response Rate (95% CI)
ProQuad	Measles	4733	97.4% (96.9%, 97.9%)
	Mumps (vaccine-type)†	973	98.8% (97.9%, 99.4%)
	Mumps (wild-type)†	3735	95.8% (95.1%, 96.4%)
	Rubella	4773	98.5% (98.1%, 98.8%)
	Varicella	4381	91.2% (90.3%, 92.0%)
M-M-R II + VARIVAX	Measles	1516	98.2% (97.4%, 98.8%)
	Mumps (vaccine-type)†	501	99.4% (98.3%, 99.9%)
	Mumps (wild-type)†	1017	98.0% (97.0%, 98.8%)
	Rubella	1528	98.5% (97.7%, 99.0%)
	Varicella	1417	94.1% (92.8%, 95.3%)

† The mumps antibody response was assessed in different studies by two slightly different assays (using wild-type or vaccine-type strains as antigens respectively).

Children who received a second dose of ProQuad
In 2 clinical trials, 1035 subjects were administered a second dose of the frozen formulation of ProQuad subcutaneously approximately 3 months after the first dose. The vaccine response rates were 99.4% for measles, 99.9% for mumps, 98.3% for rubella, and 99.4% for varicella (≥5 gpELISA units/mL). The geometric mean titers (GMTs) following the second dose of ProQuad increased approximately 2 fold each for measles, mumps, and rubella, and approximately 41 fold for varicella. In these trials, the rates of adverse experiences after the second dose of ProQuad were generally similar to, or lower than, those seen with the first dose. The fever rate was lower after the second dose than after the first dose.

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 titers to measles, mumps, rubella, and varicella.

Children who received the earlier formulation of ProQuad at 4 through 6 years of age after primary vaccination with M-M-R II and VARIVAX.
The immunogenicity and safety of the frozen formulation of ProQuad were evaluated in a clinical trial involving 799 subjects 4 through 6 years of age who had received M-M-R II and VARIVAX at least 1 month prior to study entry. Following the dose of ProQuad administered subcutaneously, GMTs for measles, mumps, rubella, and varicella were similar to those

following a second dose of M-M-R II and VARIVAX administered concomitantly at separate injection sites. Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of M-M-R II given concomitantly with placebo. In this trial, the rates and types of adverse experiences seen in the group that received ProQuad were generally similar to those seen in the control groups (see Table 2).

Table 2
Summary of Observed Antibody Responses to Measles, Mumps, Rubella and Varicella 6 weeks Following the Administration of a Primary Dose of ProQuad (Varicella Virus Potency ≥ 3.97 $\log_{10}$ PFU) in Subjects Who Had Previously Received M-M-R II and VARIVAX (Per-Protocol-Population)

Group	Antigen	n	GMT(95% CI)	Seroprotection (95% CI)
ProQuad	Measles	367	1985.9 (1817.6, 2169.9)	99.2% (97.6%, 99.8%)
	Mumps	367	206.0 (188.2, 225.4)	99.5% (98.0%, 99.9%)
	Rubella	367	217.3 (200.1, 236.0)	100% (99.0%, 100%)
	Varicella†	367	322.2 (278.9, 372.2)	98.9% (97.2%, 99.7%)
M-M-R II + VARIVAX	Measles	171	2084.3 (1852.3, 2345.5)	99.4% (96.8%, 100%)
	Mumps	171	295.9 (262.5, 333.5)	100% (97.9%, 100%)
	Rubella	171	154.1 (138.9, 170.9)	99.4% (96.8%, 100%)
	Varicella†	171	209.3 (171.2, 255.9)	99.4% (96.8%, 100%)
M-M-R II + VARIVAX	Measles	185	2046.9 (1815.2, 2308.2)	100% (98.0%, 100%)
	Mumps	185	308.5 (269.6, 352.9)	100% (98.0%, 100%)
	Rubella	185	174.0 (157.3, 192.6)	100% (98.0%, 100%)
	Varicella†	N/A	N/A	N/A

† Percent of subjects who had a postvaccination VZV antibody titer ≥5 gpELISA units/mL.

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 using the frozen formulation of ProQuad. 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 M-M-R II 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 VARIVAX, detectable varicella antibodies were present in most individuals tested for up to 10 years postvaccination.

Herpes Zoster
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 the frozen formulation of ProQuad and followed for 1 year. Both cases were unremarkable and no sequelae were reported.

The reported rate of zoster in recipients of VARIVAX appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella. In clinical trials, 12 cases of herpes zoster were reported in 9543 vaccinated individuals 12 months through 12 years of age during 84,414 person-years of follow-up. This resulted in a calculated incidence of at least 0.14 cases per 1,000 person-years. The incidence of herpes zoster following naturally acquired infection in subjects > 5 years of age and persons 5 to 9 years of age has been reported to be 1.1 and 0.51 per 1,000 person-years, respectively. All 12 cases reported after VARIVAX were mild and no sequelae were reported. The long-term effect of VARIVAX on the incidence of herpes zoster is unknown at present.

Reye Syndrome
Reye syndrome following wild-type varicella infection has occurred in children and adolescents, the majority of whom received salicylates. In clinical studies using both formulations of ProQuad and in the clinical studies of VARIVAX, physicians advised subjects not to use salicylates for 6 weeks after vaccination. There were no reports of Reye syndrome in recipients of ProQuad or VARIVAX during these studies.

Studies With Other Vaccines
In a clinical trial involving 1913 healthy subjects 12 through 15 months of age, 949 received the frozen formulation of ProQuad subcutaneously, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and *Haemophilus* b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine concomitantly at separate injection sites. Another 485 healthy subjects received ProQuad at the initial visit followed by DTaP and Haemophilus b Conjugate and Hepatitis B (Recombinant) Vaccine given concomitantly 6 weeks later. In subjects 13.5 months of age or older, seroconversion rates and antibody titers were comparable between the 2 groups at approximately 6 weeks postvaccination. However, in subjects less than 13.5 months of age, seroconversion rates and antibody titers were comparable between the 2 groups for each of the vaccine components except pertussis FHA (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS*)*. No clinically significant differences in adverse experiences were reported between the 2 treatment groups.

ProQuad administered with Pneumococcal 7-valent Conjugate Vaccine (PREVNAR[1]*)*
In a clinical trial involving 1027 healthy children 12 through 15 months of age, 510 were randomised to receive ProQuad subcutaneously and Prevnar concomitantly at separate injection sites, and 517 were randomised to receive ProQuad and Prevnar non-concomitantly. Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, and *S.pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were comparable in the concomitant and non-concomitant groups at 6 weeks post-vaccination indicating that ProQuad and Prevnar can be administered concomitantly at separate injection sites. No clinically significant differences in adverse events were reported between treatment groups.

In a clinical trial involving 1800 healthy children 12 through 23 months of age, 1453 were randomised to receive 2 doses of VAQTA, and 347 were randomised to receive 2 doses of VAQTA concomitantly with 2 doses ProQuad subcutaneously at least 6 months apart. Rates of adverse experiences were lower following a second dose than following the first dose of both vaccines given concomitantly.

ProQuad administered with Pneumococcal 7-valent Conjugate Vaccine and/or Hepatitis A (VAQTA)
In a clinical trial involving 653 healthy children 12 through 15 months of age, 330 were randomised to receive ProQuad subcutaneously and Prevnar concomitantly followed by VAQTA 6 weeks later. Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, and *S.pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were comparable between the 3 groups at 6 weeks post-vaccination indicating that ProQuad, VAQTA and Prevnar can be administered concomitantly at separate injection sites. No clinically significant differences in adverse events were reported among treatment groups.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Not applicable

[1] Trademark of Wyeth Pharmaceuticals, Inc. Licensed in Australia as Prevenar.

Distribution
Not applicable

Metabolism
Not applicable

Excretion
Not applicable

5.3 PRECLINICALSAFETY DATA

Genotoxicity
Mutagenicity
ProQuad has not been evaluated for its mutagenic potential.

Carcinogenicity
ProQuad has not been evaluated for its carcinogenic potential

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients
sucrose
hydrolysed porcine gelatin*
urea
sodium chloride
sorbitol
monosodium glutamate monohydrate
monobasic sodium phosphate
dibasic sodium phosphate
sodium bicarbonate
monobasic potassium phosphate
dibasic potassium phosphate
potassium chloride
neomycin
phenolsulfonphthalein
*contains sulfites

Diluent
Water for injections

6.2 INCOMPATIBILITIES

Not applicable. Please refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for further information.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

During shipment to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of ≤8°C, but not exceed temperatures lower than -50ºC (-58ºF). Use of dry ice may subject ProQuad to temperatures colder than -50ºC (-58ºF).

Immediately upon receipt of the vaccine shipment, the vaccine must be kept in the refrigerator at a temperature of 2°C to 8°C until ready for use. THE VACCINE SHOULD NOT BE FROZEN.

Before reconstitution, ProQuad has a shelf life of 18 months when refrigerated at 2°C to 8°C.

DO NOT STORE LYOPHILISED VACCINE AT ROOM TEMPERATURE.

IF LYOPHILISED VACCINE IS INADVERTENTLY STORED AT ROOM TEMPERATURE, IT SHOULD BE DISCARDED.

Protect the vaccine from light at all times since such exposure may inactivate the vaccine viruses.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 60 MINUTES (1 HOUR) WHEN STORED AT 20°C to 25°C OR WITHIN 150 MINUTES (2.5 HOURS) WHEN STORED AT 2°C to 8°C.

The diluent (prefilled syringe or vial) should be stored separately at room temperature (20°C to 25°C), or in the refrigerator (2°C to 8°C). **Do not freeze the diluent.**

Composite packs containing the vaccine vial and diluent:
For composite packs with the vaccine vial and diluent packaged together, store in the refrigerator at 2°C to 8°C. **DO NOT STORE THE COMPOSITE PACK IN THE FREEZER**.

6.5 NATURE AND CONTENTS OF CONTAINER

ProQuad is supplied as:

(1) a single-dose vial of lyophilised vaccine and a single-dose vial or needleless syringe of diluent supplied in a separate carton
(2) a box of five single-dose vials of lyophilised vaccine and a box of five single-dose vials or five needleless syringes of diluent supplied in a separate carton
(3) a box of ten single-dose vials of lyophilised vaccine and a box of ten single-dose vials or ten needleless syringes of diluent supplied in a separate carton
(4) a single-dose vial of lyophilised vaccine with a single-dose vial or syringe of diluent in one carton
(5) five single-dose vials of lyophilised vaccine with five single-dose vials or syringes of diluent in one carton
(6) ten single-dose vials of lyophilised vaccine and ten single-dose vials or syringes of diluent in one carton
(7) a box of ten single-dose vials of lyophilised vaccine

The frozen formulation of this product is not available.

Not all presentations and pack sizes may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Not applicable

CAS number
Not applicable

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Medicine

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

8 Feb 2007

10 DATE OF REVISION

7 January 2026

Summary table of changes

Section changed	Summary of new information
2, 3	Update to component vaccines section.
6.1	Updated to reflect presence of sulfite and to include information on the diluent.
6.4	Update to the diluent storage text to specify prefilled syringe or vials.
8	Update MSD sponsor address
Multiple	Minor editorial revisions were made throughout the document

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