Registration No.: 2C 1/61 (NBC)

Importer / Manufacturer: MSD (Thailand) Ltd. / Merck Sharp & Dohme Corp., West Point, Pennsylvania 19486, USA

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

ProQuad®
[Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live]
Refrigerator-stable formulation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ProQuad, when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 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 $\log_{10}$ PFU (plaque-forming units) of Oka/Merck varicella virus.

3. PHARMACEUTICAL FORM

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

PRODUCT DESCRIPTION
Lyophilized powder and solvent for suspension for injection.

Before reconstitution, the lyophilized powder is a white to faint yellow compact crystalline pellet and the solvent is a clear colourless liquid.

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 Posology and method of administration

Dosage
Individuals 12 months through 12 years of age should receive a single dose of ProQuad administered subcutaneously.

If a second dose of measles-containing vaccine is to be administered according to applicable official recommendations, then ProQuad may be used for this dose.

[Note: Local vaccination schedules may be substituted for the above recommendations as dictated by local authorities.]

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 1 month should elapse between a dose of ATTENUVAX or M-M-R II and 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.

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

Method of Administration
FOR SUBCUTANEOUS 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.

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.

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.

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.

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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Before reconstitution, the lyophilized vaccine is a white to pale yellow compact crystalline plug. ProQuad, when reconstituted, is a clear pale yellow to light pink liquid.

4.3 Contraindication

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

History of anaphylactoid reaction to neomycin.

Blood dyscrasias, leukemia, 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 hypogammaglobulinemic and dysgammaglobulinemic 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.

Pregnancy; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. (See **PREGNANCY**.)

4.4 Special warnings and precautions for use

General

Adequate treatment provisions, including 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.

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.

The duration of protection from measles, mumps, rubella, and varicella infection after vaccination with ProQuad is unknown.

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.

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

Post-licensing experience with VARIVAX suggests that transmission of varicella vaccine virus may occur rarely between healthy vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella, as well as high-risk individuals susceptible to varicella.
High-risk individuals susceptible to varicella include:

- Immunocompromised individuals;
- 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
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.

Post-Exposure Prophylaxis
No clinical data are available for ProQuad administered after exposure to measles, mumps, rubella, or varicella. However, post-exposure prophylaxis has been demonstrated for measles and varicella with a measles-containing vaccine and varicella-containing vaccine, respectively, when administered to the susceptible individuals within 3 days of exposure.

Females of Childbearing Age
In females of childbearing age, pregnancy should be avoided for 3 months following vaccination.

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.

4.5 Interaction with other medical products and forms of interaction

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.

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.

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.

Results from clinical studies indicate that ProQuad may be administered concomitantly with *Haemophilus* b conjugate (meningococcal protein conjugate), hepatitis B (recombinant), pneumococcal conjugate, and hepatitis A (inactivated) vaccines.

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

4.6 Pregnancy and lactation

Pregnancy

Studies have not been conducted with ProQuad in pregnant women. It is also not known whether ProQuad can cause harm to the fetus when administered to a pregnant woman or can affect reproduction capacity. Therefore, ProQuad should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see INDICATIONS, CONTRAINDICATIONS, and PRECAUTIONS).

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 fetal 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 fetal 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 fetus, there is no evidence that it causes congenital malformations in humans; (3) In a 15-year survey involving over 1100 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 635 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome; and (4) Wild-type varicella can sometimes cause harm to the fetus.

Nursing mothers

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 if ProQuad is inadvertently administered to a nursing woman.

Pediatric use

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

4.7 Effects on the ability to drive and use machines

N/A

4.8 Undesirable effects

Children 12 through 23 months of age

In clinical trials, ProQuad was administered alone to 6038 children 12 through 23 months of age. 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, roseola, viral infection, viral rash
Rare: bronchiolitis, candidiasis, infectious croup, 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, emotional changes

Nervous system disorders

Uncommon: febrile seizure, 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, rhinorrhea
Rare: wheezing

Gastrointestinal disorders
Common: diarrhea, vomiting
Rare: flatulence, nausea, teething

Skin and subcutaneous tissue disorders
Common: measles-like rash†, rash, varicella-like rash†
Uncommon: dermatitis (including contact, atopic, and diaper rash), eczema, erythema, miliaria rubra/heat rash, rubella-like rash†, urticaria, viral exanthema
Rare: acne, 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 hemorrhage, 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, non-venomous bite/sting

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 summarised below.

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

Blood and the lymphatic system disorders
aplastic anemia, lymphadenitis, regional lymphadenopathy, thrombocytopenia

Immune system disorders

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

Psychiatric disorders
apathy, nervousness

Nervous system disorders
Acute disseminated encephalomyelitis (ADEM), afebrile convulsions or seizures, aseptic meningitis (see below), Bell's palsy, cerebrovascular accident, dizziness, dream abnormality, encephalitis (see below), encephalopathy (see below), Guillain-Barré syndrome, hypersomnia, measles inclusion body encephalitis, ocular palsies, paraesthesia, polyneuritis, polyneuropathy, subacute sclerosing panencephalitis (see below), syncope, transverse myelitis, tremor
Eye disorders
edema of the eyelid, irritation, necrotizing 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, epistaxis, pneumonitis, pneumonia, pulmonary congestion, rhinitis, sinusitis, sneezing, sore throat

Gastrointestinal disorders
abdominal pain, hematochezia, mouth ulcer

Skin and subcutaneous tissue disorders
erythema multiforme, Henoch-Schönlein purpura, herpes simplex, impetigo, panniculitis, pruritus, purpura, skin induration, Stevens-Johnson syndrome, sunburn

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

General disorders and administration site conditions
injection site complaints (burning and/or stinging of short duration, eczema, edema/swelling, hive-like rash, hematoma, induration, lump, vesicles, wheal and flare), inflammation, lip abnormality, papillitis, roughness/dryness, stiffness, trauma, varicella-like rash, venipuncture site hemorrhage, warm sensation, warm to touch

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. 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.

Post-marketing surveillance of the more than 518 million doses that have been distributed worldwide (1978 to 2007) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. In no case has it been shown conclusively that reactions were actually caused by the vaccine; however, the data suggest the possibility that some of these cases may have been caused by measles vaccines. 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 2000 reported cases).

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.

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. A historical comparison group included 69,237 age-, gender-, and date-of-vaccination (day and month)-matched subjects who were given M-M-R II and VARIVAX concomitantly. The primary objective was to assess the incidence of febrile seizures occurring within various time intervals after vaccination in 12- to 60-month-old children who had neither been vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections (N=31,298 vaccinated with ProQuad, including 31,043 who were 12 to 23 months old). The incidence of febrile seizures was also assessed in a historical control group of children who had received their first vaccination with M-M-R II and VARIVAX concomitantly (N=31,298, including 31,019 who were 12 to 23 months old). The secondary

objective was to assess the general safety of ProQuad in the 30-day period after vaccination in children 12 months to 12 years old.

In pre-licensure clinical studies, an increase in fever was observed 5 to 12 days after vaccination with ProQuad (dose 1) compared to M-M-R II and VARIVAX (dose 1) given concomitantly. In the post-marketing observational surveillance study, results from the primary safety analysis revealed an approximate two-fold increase in the risk of febrile seizures in the same 5 to 12 day timeframe after vaccination with ProQuad (dose 1). The incidence of febrile seizures 5 to 12 days after ProQuad (dose 1) (0.70 per 1000 children) was higher than that in children receiving M-M-R II and VARIVAX concomitantly (0.32 per 1000 children) [relative risk (RR) 2.20, 95% confidence interval (CI): 1.04, 4.65]. The incidence of febrile seizures 0 to 30 days after ProQuad (dose 1) (1.41 per 1000 children) was similar to that observed in children receiving M-M-R II and VARIVAX concomitantly [RR 1.10 (95% CI: 0.72, 1.69)]. See Table 1. General safety analyses revealed that the risks of fever (RR=1.89; 95% CI: 1.67, 2.15) and skin eruption (RR=1.68; 95% CI: 1.07, 2.64) were significantly higher after ProQuad (dose 1) compared with those who received concomitant first doses of M-M-R II and VARIVAX, respectively. All medical events that resulted in hospitalization or emergency room visits were compared between the group given ProQuad and the historical comparison group, and no other safety concerns were identified in this study.

Table 1
Confirmed Febrile Seizures Days 5 to 12 and 0 to 30 After Vaccination with ProQuad (dose 1) Compared to Concomitant Vaccination with M-M-R II and VARIVAX (dose 1) in Children 12 to 60 Months of Age

Time period	ProQuad cohort (N=31,298)		MMR+V cohort (N=31,298)		Relative risk (95% CI)
	n	Incidence per 1000	n	Incidence per 1000	
5 to 12 days	22	0.70	10	0.32	2.20 (1.04, 4.65)
0 to 30 days	44	1.41	40	1.28	1.10 (0.72, 1.69)

In this observational post-marketing study, no case of febrile seizure was observed during the 5 to 12 day post-vaccination time period among 26,455 children who received ProQuad as a second dose of M-M-R II and/or VARIVAX (25,212 as second dose of M-M-R II and VARIVAX, 1,056 as a second dose of M-M-R II, and 187 as a second dose of VARIVAX). In addition, detailed general safety data were available from the 25,212 children who received ProQuad as a second dose of M-M-R II and VARIVAX, most of them (95%) between 4 and 6 years of age, and an analysis of these data by an independent, external safety monitoring committee did not identify any specific safety concern.

4.9 Overdose

There are no data with regard to overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral Vaccine

ATC code: J07BD54

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.

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, 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 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. Clinical trials also established that the earlier formulation of ProQuad is similar to the individual component vaccines (M-M-R II and VARIVAX), which are 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. 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.

Children who received a second dose of ProQuad

In 2 clinical trials, 1035 subjects were administered a second dose of ProQuad approximately 3 months after the first dose. The vaccine response rates were 99.4% for measles, 99.9% for mumps, 98.3% for rubella, and 99.4% for varicella (≥5 gpELISA units/mL). The geometric mean titers (GMTs) following the second dose of ProQuad increased approximately 2 fold each for measles, mumps, and rubella, and approximately 41 fold for varicella. 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 ProQuad at 4 through 6 years of age after primary vaccination with M-M-R II and VARIVAX

The immunogenicity and safety 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, 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.

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 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 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.

Post-Exposure Prophylaxis

No clinical data are available for ProQuad 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.

Reye Syndrome

Reye syndrome following wild-type varicella infection has occurred in children and adolescents, the majority of whom had received salicylates. In clinical studies 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 ProQuad, 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 **DRUG INTERACTIONS***).* No clinically significant differences in adverse experiences were reported between the 2 treatment groups.

In a clinical trial involving 1027 healthy children 12 to 15 months of age, 510 were randomized to receive ProQuad and Prevnar concomitantly at separate injection sites, and 517 were

randomized 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 to 23 months of age, 1453 were randomized to receive 2 doses of VAQTA, and 347 were randomized to receive 2 doses of VAQTA concomitantly with 2 doses ProQuad 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.

In a clinical trial involving 653 healthy children 12 to 15 months of age, 330 were randomized to receive VAQTA, ProQuad, and Prevnar concomitantly, and 323 were randomized to receive ProQuad 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.

In the above 3 post-licensure clinical trials evaluating the concomitant use of ProQuad with other pediatric 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.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

N/A

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N/A

6.2 Incompatibilities

N/A

6.3 Shelf life

18 months

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 2 to 8°C (36 to 46°F) or colder.

Before reconstitution, store the lyophilized vaccine in a refrigerator at 2 to 8°C (36 to 46°F) or colder. The vaccine may also be stored in a freezer and subsequently transferred to a refrigerator; however, the lyophilized vaccine should not be refrozen.

DO NOT STORE LYOPHILIZED VACCINE AT ROOM TEMPERATURE.

IF LYOPHILIZED 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 30 MINUTES.

The diluent should be stored separately at room temperature (20 to 25°C, 68 to 77°F), or in the refrigerator (2 to 8°C, 36 to 46°F).

6.5 Nature and content of container

ProQuad is supplied as a single dose vial (0.5 mL) of lyophilized vaccine and a vial (0.7 mL) of diluent.
ProQuad is supplied as 5 single dose vials (0.5 mL) of lyophilized vaccine and 5 vials (0.7 mL) of diluent.
ProQuad is supplied as 10 single dose vials (0.5 mL) of lyophilized vaccine and 10 vials (0.7 mL) of diluent.

6.6 Special precautions for disposal and other handling

N/A

7. MARKETING AUTHORISATION HOLDER

MSD (Thailand) Ltd.
Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORAISATION/RENEWAL OF THE AUTHORISATION

17-Jan-2018

10. DATE OF REVISION OF THE TEXT

Jan-2018