

PRODUCT MONOGRAPH

ProQuad[®]

(Measles, Mumps, Rubella and Varicella Virus Vaccine Live)

Lyophilized powder for injection
(0.5 mL/dose after reconstitution)

Active Immunizing Agent Against
Measles, Mumps, Rubella and Varicella

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ProQuad[®]

(measles, mumps, rubella and varicella virus vaccine live)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Lyophilized powder for injection Immunogens: Measles $\geq 3.00 \log_{10} \text{TCID}_{50}$ (50% tissue culture infectious dose) Mumps $\geq 4.30 \log_{10} \text{TCID}_{50}$ Rubella $\geq 3.00 \log_{10} \text{TCID}_{50}$ Varicella $\geq 3.99 \log_{10} \text{PFU}$	Hydrolyzed gelatin Neomycin MRC-5 cell residuals <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

DESCRIPTION

ProQuad[®] (measles, mumps, rubella and varicella virus vaccine live) 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, attenuated, Merck Std.): 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, attenuated [Oka/Merck], the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells [hereafter referred to as VARIVAX[®] (varicella virus vaccine, live, attenuated [Oka/Merck]).

INDICATIONS AND CLINICAL USE

ProQuad[®] is a vaccine indicated for the prevention of measles, mumps, rubella, and varicella in children 12 months through 6 years of age. Efficacy has not been evaluated in subjects above 6 years of age.

ProQuad[®] may be used in individuals up to 12 years of age based upon the established efficacy of the separate component vaccines, M-M-R[®] II and VARIVAX[®].

CONTRAINDICATIONS

- History of hypersensitivity to any component of the vaccine, including gelatin. *For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.*
- History of anaphylactoid or anaphylactic 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, 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 WARNINGS AND PRECAUTIONS, Pregnant Women).

WARNINGS AND PRECAUTIONS

General

Administer ProQuad[®] subcutaneously; do not give intravenously.

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reactions 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 alerted to the temperature elevation that may occur following vaccination (see ADVERSE REACTIONS).

Administration of ProQuad[®] (dose 1) to children 12 to 23 months old was associated with higher rates of fever and febrile seizures at 5 to 12 days after vaccination when compared to children vaccinated with M-M-R[®] II and VARIVAX[®] administered separately (see ADVERSE REACTIONS).

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 CONTRAINDICATIONS).

The duration of protection from measles, mumps, rubella, and varicella infection after vaccination with ProQuad[®] is unknown (see ACTION AND CLINICAL PHARMACOLOGY).

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 SPECIAL POPULATIONS, Nursing Women).

There are no reports of transmission of the more attenuated Enders' Edmonston strain of measles virus or the JERYL LYNN[®] strain of mumps virus from vaccine recipients to susceptible contacts.

Post-marketing experience 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 (see 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.

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.¹

Females of Childbearing Age

In females of childbearing age, pregnancy should be avoided for 3 months following vaccination (see SPECIAL POPULATION, Pregnant Women).

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.

Hematologic

Thrombocytopenia

In clinical trials, no cases were reported regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad[®]. However, 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 ADVERSE REACTIONS).

Sensitivity/Resistance

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.²

Special Populations

Pregnant Women

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 AND CLINICAL USE, CONTRAINDICATIONS and WARNINGS 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 (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;⁴ and (4) Wild-type varicella can sometimes cause harm to the fetus.

Nursing Women

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.

Pediatrics (<12 months of age)

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

ADVERSE REACTIONS

Clinical Trial Adverse Vaccine Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying vaccine-related adverse events and for approximating rates.

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 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 $\leq 0.02\%$). Several adverse experiences were solicited in the clinical studies and are designated with the symbol (†).

[Very common ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1000$, $< 1/100$); Rare ($\geq 1/10,000$, $< 1/1000$)]

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:

Common: irritability

Uncommon: crying, insomnia, sleep disorder

Rare: agitation, clinging, emotional changes

Nervous system disorders:

Uncommon: febrile seizure, somnolence

Rare: ataxia, headache, lethargy

Ophthalmologic:

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:

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 (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:

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 (see CONTRAINDICATIONS), ocular palsies, paraesthesia, polyneuritis, polyneuropathy, subacute sclerosing panencephalitis (see below), syncope, transverse myelitis, tremor

Ophthalmologic:

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 (see CONTRAINDICATIONS), pneumonia, pulmonary congestion, rhinitis, sinusitis, sneezing, sore throat

Gastrointestinal:

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, acute hemorrhagic edema of infancy

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 (see 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 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.

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.

DRUG INTERACTIONS

Overview

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 [Varicella-Zoster Immune Globulin]).^{2,6}

Following administration of ProQuad[®], any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination.^{2,6}

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 (see ACTION AND CLINICAL PHARMACOLOGY, Reye Syndrome).

The data are not sufficient to support concomitant vaccination with diphtheria, tetanus and acellular pertussis vaccine (see ACTION AND CLINICAL PHARMACOLOGY, Studies with Other Vaccines).

Results from clinical studies indicate that ProQuad[®] may be administered concomitantly at separate injection sites 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Individuals 12 months through 12 years of age should receive a single dose of ProQuad[®] administered subcutaneously. The first dose is usually administered at 12 to 15 months of age but may be given anytime through 12 years of age.

If a second dose of measles, mumps, rubella, and varicella vaccine is needed, ProQuad[®] may be used for this second dose. Refer to the most current Canadian Immunization recommendations. The second dose is usually administered at 4 to 6 years of age. At least 1 month should elapse between a dose of a measles-containing vaccine such as M-M-R[®] II and a dose of ProQuad[®]. At least 1 month should elapse between a dose of varicella-containing vaccine and ProQuad[®].

Do not give immune globulin (IG) or Varicella Zoster Immune Globulin (VZIG) concomitantly with ProQuad[®] (see DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

Each 0.5-mL dose contains not less than 3.00 log₁₀ TCID₅₀ (50% tissue culture infectious dose) of measles virus; 4.30 log₁₀ TCID₅₀ of mumps virus; 3.00 log₁₀ TCID₅₀ of rubella virus; and a minimum of 3.99 log₁₀ PFU (plaque-forming units) of Oka/Merck varicella virus.

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.

Use With Other Vaccines:

Use different injection sites to administer each vaccine if other vaccines are administered concomitantly (see DRUG INTERACTIONS).

Reconstitution:

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. 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.

Table 2 – Reconstitution of ProQuad[®]

Single Dose Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per 0.5 mL
3 mL	Entire contents (approximately 0.7 mL)	0.5 mL	Lyophilized powder reconstituted for injection. Immunogens: Measles $\geq 3.00 \log_{10}$ TCID ₅₀ (50% tissue culture infectious dose) Mumps $\geq 4.30 \log_{10}$ TCID ₅₀ Rubella $\geq 3.00 \log_{10}$ TCID ₅₀ Varicella $\geq 3.99 \log_{10}$ PFU

OVERDOSAGE

There are no data with regard to overdose.

For management of a suspected overdose, contact your regional Poison Control Centre

ACTION AND CLINICAL PHARMACOLOGY

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.

Varicella is a highly communicable disease in children, adolescents, and adults caused by the varicella-zoster virus. The disease usually consists of 300 to 500 maculopapular and/or vesicular lesions accompanied by a fever [oral temperature ≥ 37.7 °C] in up to 70% of individuals. In Canada, it is estimated that about 350,000 cases occur each year and that 1871 of them will require hospitalization (complicated cases). Approximately 3.5 million cases of varicella occurred annually from 1980–1994 in the United States with the peak incidence occurring in children five to nine years of age. The incidence rate of chickenpox is 8.3–9.1% per year in children one to nine years of age. The attack rate of wild-type varicella following household exposure among healthy susceptible children was shown to be 87%. Although it is generally a benign, self-limiting disease, varicella may be associated with serious complications (e.g., bacterial superinfection, pneumonia, encephalitis, Reye Syndrome), and/or death. In Canada, during 1994 and 1995, a total of 24 deaths were reported to be caused by chickenpox.

Varicella-zoster virus (VZV) infection is associated with a 58-fold (95% confidence interval [CI]: 40, 85) increased risk of acquiring invasive Group A Streptococcal (GAS) disease in children. Children with invasive GAS disease and recent chickenpox were more likely to have necrotizing fasciitis (NF) [RR: 6.3; 95% CI: 1.8, 22.3].

Mechanism of Action

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, Merck Std.): 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, attenuated [Oka/Merck], the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells (hereafter referred to as VARIVAX[®]).

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.^{5,8,9} Vaccination against measles, mumps, and rubella has led to a significant reduction in the incidence of these diseases.⁹⁻¹² 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.¹³ Long-term estimated efficacy for the vaccine against all forms of varicella over 10 years was 94%.¹⁴ 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[®].

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.¹⁶ 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[®], along with Diphtheria and Tetanus Toxoid and Acellular Pertussis Vaccine Adsorbed (DTaP) as well as *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 as well as *Haemophilus b* Conjugate and Hepatitis B (Recombinant) Vaccine given concomitantly, 6 weeks later. The data are not sufficient to support concomitant vaccination with diphtheria and tetanus toxoids and acellular

pertussis vaccine adsorbed (see CLINICAL TRIALS).

ProQuad[®] may be administered concomitantly with *Haemophilus* b Conjugate and hepatitis B (recombinant) vaccines at separate injection sites. Response rates for measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, and hepatitis B were not inferior in children given ProQuad[®] plus *Haemophilus influenzae* type b conjugate and hepatitis B (recombinant) vaccines concomitantly when compared to ProQuad[®] at the initial visit and *Haemophilus influenzae* type b conjugate and hepatitis B (recombinant) vaccines given concomitantly 6 weeks later. In a clinical trial involving 1027 healthy children 12 to 15 months of age, 510 were randomized to receive ProQuad[®] and Plevnar* concomitantly at separate injection sites, and 517 were randomized to receive ProQuad[®] and Plevnar* 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 Plevnar* 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 appear to be lower following a second dose than following the first dose of both vaccines given concomitantly. However, as no formal statistical comparisons were made between treatment groups or between the randomized and nonrandomized groups in this study, the conclusions should be considered with caution due to the study design and limitations.

In a clinical trial involving 653 healthy children 12 to 15 months of age, 330 were randomized to receive VAQTA[®], ProQuad[®], and Plevnar* concomitantly, and 323 were randomized to receive ProQuad[®] and Plevnar* 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 2 groups at 6 weeks post-vaccination indicating that ProQuad[®], VAQTA[®], and Plevnar* can be administered concomitantly at separate injection sites.

The safety profile of VAQTA[®] administered concomitantly with ProQuad[®] and Plevnar* (Group 1) was generally comparable to that administered separately from ProQuad[®] and Plevnar* (Group 2). However, during Days 1 to 14 after any dose of VAQTA[®], the proportion of subjects with at least 1 adverse experience was lower in Group 2 than that in Group 1 (60.1% vs. 70.0%); a lower rate of systemic adverse experiences (46.5% vs. 61.8%) and of vaccine-related systemic adverse experiences (17.8% vs. 37.3%) was also observed in Group 2 compared with those in Group 1. The most common systemic adverse experience was pyrexia (18.5% in Group 2 vs. 38.2% in Group 1).

In the above 3 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.

Special Populations and Conditions

Pediatrics

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

Duration of Effect

The duration of protection from measles, mumps, rubella, and varicella infection after vaccination with ProQuad[®] is unknown (see ACTION AND CLINICAL PHARMACOLOGY).

STORAGE AND STABILITY

During shipment, to ensure that there is no loss of potency, ProQuad[®] must be maintained at a temperature between -50 °C and +8 °C. Use of dry ice may subject ProQuad[®] to temperatures colder than -50 °C.

Before reconstitution, ProQuad[®] should be stored refrigerated at a temperature of 2 °C to 8 °C. The vaccine may also be stored in a freezer at temperatures above -50 °C; if subsequently transferred to a refrigerator, the vaccine may be placed back in the freezer.

ProQuad[®] can be administered provided total (cumulative multiple excursions) time out of refrigeration (prior to reconstitution, at temperatures between 8 °C and 25 °C) does not exceed 14 hours. These are not, however, recommendations for storage.

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

Before reconstitution, store the vial of lyophilized vaccine at 2 °C to 8 °C or colder (above -50 °C). The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature.

Reconstituted Solutions

To maintain the potency, it is imperative that only the sterile diluent for Merck Sharp & Dohme Corp., live, attenuated virus vaccines (Sterile Water) be used for reconstitution and injection.

Use **AS SOON AS POSSIBLE** after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at room temperature. Do not freeze reconstituted vaccine. Discard if not used **within 30 minutes**.

SPECIAL HANDLING INSTRUCTIONS

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES. DO NOT FREEZE THE RECONSTITUTED VACCINE.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ProQuad[®] is supplied as follows:

Pack of 1 single-dose vial: (1) a single-dose vial of lyophilized vaccine; and (2) a separate package of 1 vial of diluent.

Pack of 10 single-dose vials: (1) a package of 10 single-dose vials of lyophilized vaccine; and (2) a separate package of 10 vials of diluent.

CHEMISTRY

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, attenuated, Merck Std.): 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, attenuated [Oka/Merck], the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells (hereafter referred to as VARIVAX[®]).

COMPOSITION

a. Active Ingredients

ProQuad[®], when reconstituted as directed, is a sterile preparation for subcutaneous administration. Each 0.5-mL dose contains not less than 3.00 log₁₀ TCID₅₀ (50% tissue culture infectious dose) of measles virus; 4.30 log₁₀ TCID₅₀ of mumps virus; 3.00 log₁₀ TCID₅₀ of rubella virus; and a minimum of 3.99 log₁₀ PFU (plaque-forming units) of Oka/Merck varicella virus.

b. Inactive Ingredients

Each 0.5-mL dose of the vaccine contains no more than 20 mg of sucrose, 11 mg of hydrolyzed gelatin, 2.5 mg of urea, 2.3 mg of sodium chloride, 16 mg of sorbitol, 0.38 mg of monosodium L-glutamate, 1.4 mg of sodium phosphate, 0.25 mg of recombinant human albumin (rHA), 0.13 mg of sodium bicarbonate, 94 mcg of potassium phosphate, 58 mcg of potassium chloride, residual components of MRC-5 cells including DNA and protein, 5 mcg of neomycin, bovine serum albumin (0.5 mcg), and other buffer and media ingredients. The 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 product is latex free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ProQuad[®]

Immunogens: Each 0.5-mL dose contains not less than 3.00 log₁₀ TCID₅₀ (50% tissue culture infectious dose) of measles virus; 4.30 log₁₀ TCID₅₀ of mumps virus; 3.00 log₁₀ TCID₅₀ of rubella virus; and a minimum of 3.99 log₁₀ PFU (plaque-forming units) of Oka/Merck varicella virus.

Product Characteristics

ProQuad[®] is a sterile lyophilized preparation of the components of measles, mumps, and rubella vaccine live and varicella vaccine, live, attenuated [Oka/Merck].

When reconstituted as directed, each dose of 0.5 mL contains:

Live attenuated measles virus (more attenuated Enders' Edmonston strain) ¹ :	not less than 3.00 log ₁₀ TCID ₅₀ [†]
Live attenuated mumps virus (JERYL LYNN [®] (Level B) strain) ² :	not less than 4.30 log ₁₀ TCID ₅₀
Live attenuated rubella virus (Wistar RA 27/3 strain) ³ :	not less than 3.00 log ₁₀ TCID ₅₀
Live attenuated varicella virus (Oka/Merck strain) ⁴ :	not less than 3.99 log ₁₀ PFU‡

[†]50% tissue culture infectious dose

‡Plaque-forming units

¹The measles virus is produced in chick embryo cell culture.

²The mumps virus is produced in chick embryo cell culture.

³The rubella virus is produced in WI-38 human diploid lung fibroblasts.

⁴The varicella virus is produced in human diploid cells (MRC-5).

CLINICAL TRIALS

Study demographics and trial design

Table 3 – Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age
009	Partially blind, randomized [‡]	ProQuad [®] and Placebo Dosage: 0.5 mL Route of administration: Subcutaneous Duration: ProQuad [®] on Day 0 and Day 90, placebo on Day 0 M-M-R [®] II and VARIVAX [®] Dosage: 0.5 mL Route of administration: Subcutaneous Duration: Day 0	480 total	14.1 months
011	Partially double-blind, randomized [§]	ProQuad [®] (low, medium and high varicella potency) Dosage: 0.5 mL Route of administration: Subcutaneous Duration: Day 0 and Day 90 M-M-R [®] II and VARIVAX [®] Dosage: 0.5 mL Route of administration: Subcutaneous Duration: Day 0	1559 total	12.9 months
012	Partially double-blind, randomized	ProQuad [®] (3 consistency lots) Dosage: 0.5 mL Route of administration: Subcutaneous Duration: Day 0 M-M-R [®] II and VARIVAX [®] Dosage: 0.5 mL Route of administration: Subcutaneous Duration: Day 0	3928 total	12.7 months

[‡] Subjects were blinded for the first dose only.

[§] Subjects were blinded to the formulation of ProQuad[®] received.

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age
013	Open, randomized	<p>Group 1 Dosage: 0.5 mL Route of administration: Subcutaneous (ProQuad[®]), Intramuscular (Comvax* and Tripedia*) Duration: ProQuad[®], Comvax* and Tripedia* on Day 0</p> <p>Group 2 Dosage: 0.5 mL Route of administration: Subcutaneous (ProQuad[®]), Intramuscular (Comvax* and Tripedia*) Duration: ProQuad[®] on Day 0, Comvax* and Tripedia* on Day 42</p> <p>Group 3 Dosage: 0.5 mL Route of administration: Subcutaneous (M-M-R[®] II AND VARIVAX[®]), Intramuscular (Comvax* and Tripedia*) Duration: M-M-R[®] II and VARIVAX[®] on Day 0, Comvax* and Tripedia* on Day 42</p>	1915 total	12.4 months
014	Double-blind, randomized	<p>Group 1 Dosage: 0.5 mL Route of administration: Subcutaneous Duration: ProQuad[®] and placebo on Day 0</p> <p>Group 2 Dosage: 0.5 mL Route of administration: Subcutaneous Duration: M-M-R[®] II and placebo on Day 0</p> <p>Group 3 Dosage: 0.5 mL Route of administration: Subcutaneous Duration: M-M-R[®] II and VARIVAX[®] on Day 0</p>	800 total	4.3 years

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age
016	ProQuad [®] Frozen vs. ProQuad [®] Refrigerator- Stable Double-blind, randomized	Group 1 Dosage 0.5 mL: ProQuad [®] refrigerator- stable Group 2 Dosage 0.5 mL: ProQuad [®] (frozen) Route of administration: Subcutaneous Duration: ProQuad [®] refrigerator-stable and ProQuad [®] (frozen) on Day 1	1542 total	12.8 months
019	Open label, randomized	Group 1 Dosage 0.5 mL: ProQuad [®] + Prevnar* (4 th dose) and a second dose of ProQuad [®] at least 90 days after the first dose Group 2 Dosage 0.5 mL: fourth dose of Prevnar* on Day 1 and received ProQuad [®] on Day 43. Subjects in Group 2 received a second dose of ProQuad [®] at least 90 days after the first dose Group 3 Dosage 0.5 mL: ProQuad [®] on Day 1 and a fourth dose of Prevnar* on Day 43. Subjects in Group 3 received a second dose of ProQuad [®] at least 90 days after the first dose (Day 91 + 90 days) Route of administration: Subcutaneous: ProQuad [®] Intramuscular: Prevnar* Duration: as above	1027 total	12.6 months
066	Open, randomized	Group 1 Dosage 0.5 mL: First dose of VAQTA [®] on Day 1 (~12 to 17 months of age), and the second dose of VAQTA [®] at least 6 months after the first dose at Week 24 up to Week 51 (~18 to 23 months of age) depending upon the age at Visit 1. Group 2 Dosage 0.5 mL: Received both doses of VAQTA [®] + ProQuad [®] concomitantly but at separate injection sites on Day 1 (~12 to 17 months of age), and second doses at Week 24 up to Week 51 (~18 to 23 months of age) depending upon the age at Visit 1. Both doses of ProQuad [®] and VAQTA [®] were administered at least 6 months apart and before 24 months of age. Route of administration: Subcutaneous: ProQuad [®] Intramuscular: VAQTA [®] Duration: as above	1800 total	13.2 months

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age
067	Open, randomized	<p>Dosage 0.5ml:</p> <p>Group 1: On Day 1, VAQTA[®] + ProQuad[®] + Prevnar* were administered concomitantly at separate injection sites. At Week 24, second doses of VAQTA[®] and ProQuad[®] were administered concomitantly at separate injection sites.</p> <p>Group 2: was administered at 4 separate study visits. On Day 1, ProQuad[®] + Prevnar* were administered concomitantly at separate injection sites. At Week 6, only VAQTA[®] was administered. At Week 30, the second dose of VAQTA[®] was administered. At Week 34, the second dose of ProQuad[®] was administered.</p> <p>Route of administration: Subcutaneous: ProQuad[®] Intramuscular: VAQTA[®] and Prevnar*</p> <p>Duration: as above</p>	653 total	12.4 months

Study results

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 frozen formulation of ProQuad[®] in one clinical trial. The four other 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.

Immunogenicity in Children 12 to 23 Months of Age After a Single Dose

In 4 randomized clinical trials, 5446 healthy children 12 to 23 months of age were administered ProQuad[®], and 2038 children were vaccinated with M-M-R[®] II and VARIVAX[®] given concomitantly at separate injection sites. Subjects enrolled in each of these trials had a negative clinical history, no known recent exposure, and no vaccination history for varicella, measles, mumps, and rubella. Children were excluded from study participation if they had an immune impairment or had a history of allergy to components of the vaccine(s). Except for in 1 trial (see [ProQuad[®] Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine] below), no concomitant vaccines were permitted during study participation. The race distribution of the study subjects across these studies following a first dose of ProQuad[®] was as follows: 66.3% White; 12.7% African-American; 9.9% Hispanic; 6.7% Asian/Pacific; 4.2% other; and 0.2% American Indian. The gender distribution of the study subjects across these studies following a first dose of ProQuad[®] was 52.6% male and 47.4% female. A summary of combined immunogenicity results 6 weeks following administration of a single dose of

ProQuad[®] or M-M-R[®] II and VARIVAX[®] is shown in Table 4. These results were similar to the immune response rates induced by concomitant administration of single doses of M-M-R[®] II and VARIVAX[®] at separate injection sites (lower bound of the 95% CI for the risk difference in measles, mumps, and rubella seroconversion rates were >-5.0 percentage points and the lower bound of the 95% CI for the risk difference in varicella seroprotection rates was either >-15 percentage points [one study] or >-10.0 percentage points [three studies]).

Table 4 – Summary of Combined Immunogenicity Results 6 Weeks Following the Administration of a Single Dose of ProQuad[®] (Varicella Virus Potency $\geq 3.97 \log_{10}$ PFU) or M-M-R[®] II and VARIVAX[®] (Per-Protocol Population)

Group	Antigen	n	Observed Response Rate (95% CI)	Observed GMT (95% CI)
ProQuad [®] (N=5446 [†])	Varicella	4381	91.2% (90.3%, 92.0%)	15.5 (15.0, 15.9)
	Measles	4733	97.4% (96.9%, 97.9%)	3124.9 (3038.9, 3213.3)
	Mumps (OD cutoff) [‡]	973	98.8% (97.9%, 99.4%)	105.3 (98.0, 113.1)
	Mumps (wild-type ELISA) [‡]	3735	95.8% (95.1%, 96.4%)	93.1 (90.2, 96.0)
	Rubella	4773	98.5% (98.1%, 98.8%)	91.8 (89.6, 94.1)
M-M-R [®] II + VARIVAX [®] (N=2038 [†])	Varicella	1417	94.1% (92.8%, 95.3%)	16.6 (15.9, 17.4)
	Measles	1516	98.2% (97.4%, 98.8%)	2239.6 (2138.3, 2345.6)
	Mumps (OD cutoff) [‡]	501	99.4% (98.3%, 99.9%)	87.5 (79.7, 96.0)
	Mumps (wild-type ELISA) [‡]	1017	98.0% (97.0%, 98.8%)	90.8 (86.2, 95.7)
	Rubella	1528	98.5% (97.7%, 99.0%)	102.2 (97.8, 106.7)

[†] Includes ProQuad[®] + Placebo followed by ProQuad[®] (Visit 1) [Protocol 009], ProQuad[®] Middle and High Doses (Visit 1) [Protocol 011], ProQuad[®] (Lot 1, Lot 2, Lot 3) [Protocol 012], both the Concomitant and Non-concomitant groups (Protocol 013).
[‡] The mumps antibody response was assessed by a vaccine-strain ELISA in Protocols 009 and 011 and by a wild-type ELISA in Protocols 012 and 013. In the former assay, the serostatus was based on the OD cutoff of the assay. In the latter assay, 10 mumps ELISA units was used as the serostatus cutoff.
n = Number of per-protocol subjects with evaluable serology.
CI = Confidence interval.
GMT = Geometric mean titer.
ELISA = Enzyme-linked immunosorbent assay.
PFU = Plaque-forming units.
OD = Optical density.

Immunogenicity of the refrigerator-stable formulation of ProQuad[®] (N=1006) was compared with that of the frozen formulation of ProQuad[®] (N=513) for 42 days postvaccination in children 12 through 23 months of age. Statistical analysis of non-inferiority in antibody response rates and GMTs to measles, mumps, rubella, and varicella, at 6 weeks postvaccination is presented in Table 5. The immunogenicity of the refrigerator-stable formulation and the frozen formulation of ProQuad[®] were shown to be similar.

Table 5 – Statistical Analysis of Non-Inferiority in Antibody Response Rates and GMTs to Measles, Mumps, Rubella, and VZV, at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella, or With a VZV Antibody Titer <1.25 gpELISA Units/mL at Baseline Following Vaccination With Refrigerator-Stable ProQuad® vs. Frozen ProQuad® in Children 12 to 23 Months of Age (Per-Protocol Analysis)

Assay	Parameter	ProQuad® (Refrigerator-Stable) (N=1006)		ProQuad® (Frozen) (N=513)		Risk Difference (Percentage Points) ^{†,‡} / Fold-Difference ^{†,§} (95% CI)
		n	Estimated Response [†]	n	Estimated Response [†]	
Measles	% ≥255 mIU/mL GMT	879	99.1% 2412.2	452	98.5% 2409.3	0.6 (-0.5, 2.3) 1.0 (0.9, 1.1)
Mumps	% ≥10 Ab Units GMT	883	97.7% 118.7	447	98.0% 116.8	-0.3 (-1.8, 1.6) 1.0 (0.9, 1.1)
Rubella	% ≥10 IU/mL GMT	908	99.6% 97.1	464	99.6% 93.5	-0.0 (-0.8, 1.2) 1.0 (1.0, 1.1)
Varicella	% ≥5 gpELISA Units/mL GMT	839	90.1% 12.3	430	88.8% 11.8	1.3 (-2.2, 5.1) 1.0 (0.9, 1.1)

[†] Estimated responses and their risk difference/fold-difference were based on a statistical analysis model adjusting for study centers.

[‡] [ProQuad® (Refrigerator-Stable) – ProQuad® (Frozen)].

[§] [ProQuad® (Refrigerator-Stable)/ProQuad® (Frozen)].

The conclusion of non-inferiority of response rates is based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -5 percentage points for measles, mumps, and rubella response rates and being greater than -10 percentage points for the VZV response rate (*i.e.*, excluding a decrease equal to or more than the pre-specified criterion of either 5 or 10 percentage points). This indicates that the risk difference is statistically significantly less than the pre-specified clinically relevant decrease of 5.0 or 10.0 percentage points at the 1-sided alpha = 0.025 level. The conclusion of non-inferiority of GMTs is based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.67 (*i.e.*, excluding a decrease of 1.5-fold or more). This indicates that the fold-difference is statistically significantly less than the pre-specified clinically relevant 1.5-fold difference at the 1-sided alpha = 0.025 level.

N = Number of subjects vaccinated in each treatment group.

n = Number of subjects with measles antibody titers <255 mIU/mL, mumps antibody titers <10 ELISA Ab Units, rubella antibody titers <10 IU/mL, or VZV antibody titers <1.25 gpELISA units/mL at baseline and with postvaccination serology contributing to the per-protocol analysis.

ELISA = Enzyme-linked immunosorbent assay.

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

CI = Confidence interval.

VZV = Varicella-zoster virus.

Immunogenicity in Children 15 to 31 Months of Age After a Second Dose of ProQuad®

In 2 of the randomized clinical trials described above, a subgroup (N=1035) of the 5446 children administered a single dose of ProQuad® were administered a second dose of ProQuad® approximately 3 to 9 months after the first dose. Children were excluded from receiving a second dose of ProQuad® if they were recently exposed to or developed varicella, measles, mumps, and/or rubella prior to receipt of the second dose. No concomitant vaccines were administered to these children. The race distribution across these studies following a second dose of ProQuad® was as follows: 67.3% White; 14.3% African-American; 8.3% Hispanic; 5.4% Asian/Pacific; 4.4% other; 0.2% American Indian; and 0.10% mixed. The gender distribution of the study subjects across these studies following a second dose of ProQuad® was 50.4% male and 49.6% female.

A summary of immune responses following a second dose of ProQuad® is presented in Table 6.

Results from this study showed that 2 doses of ProQuad[®] administered at least 3 months apart elicited a positive antibody response to all four antigens in greater than 98% of subjects. 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.

Table 6 – Summary of Immune Response to a First and Second Dose of ProQuad[®] in Subjects <3 Years of Age Who Received ProQuad[®] with a Varicella Virus Dose $\geq 3.97 \log_{10}$ PFU[†]

Antigen	Serostatus Cutoff/ Response Criteria	Dose 1 N=1097			Dose 2 N=1097		
		n	Observed Response Rate (95% CI)	Observed GMT (95% CI)	n	Observed Response Rate (95% CI)	Observed GMT (95% CI)
Measles	≥ 120 mIU/mL [‡]	915	98.1% (97.0%, 98.9%)	2956.8 (2786.3, 3137.7)	915	99.5% (98.7%, 99.8%)	5958.0 (5518.9, 6432.1)
	≥ 255 mIU/mL	943	97.8% (96.6%, 98.6%)	2966.0 (2793.4, 3149.2)	943	99.4% (98.6%, 99.8%)	5919.3 (5486.2, 6386.6)
Mumps	\geq OD Cutoff (ELISA antibody units)	920	98.7% (97.7%, 99.3%)	106.7 (99.1, 114.8)	920	99.9% (99.4%, 100%)	253.1 (237.9, 269.2)
Rubella	≥ 10 IU/mL	937	97.7% (96.5%, 98.5%)	91.1 (85.9, 96.6)	937	98.3% (97.2%, 99.0%)	158.8 (149.1, 169.2)
Varicella	<1.25 to ≥ 5 gpELISA Units	864	86.6% (84.1%, 88.8%)	11.6 (10.9, 12.3)	864	99.4% (98.7%, 99.8%)	477.5 (437.8, 520.7)
	\geq OD Cutoff (gpELISA)	695	87.2% (84.5%, 89.6%)	11.6 (10.9, 12.4)	695	99.4% (98.5%, 99.8%)	478.7 (434.8, 527.1)

[†] Includes the following treatment groups: ProQuad[®] + Placebo followed by ProQuad[®] (Visit 1) [Protocol 009] and ProQuad[®] (Middle and High Dose) [Protocol 011].

[‡] Samples from Protocols 009 and 011 were assayed in the legacy format Measles ELISA, which reported antibody titers in Measles ELISA units. To convert titers from ELISA units to mIU/mL, titers for these 2 protocols were divided by 0.1025. The lowest measurable titer postvaccination is 207.5 mIU/mL. The response rate for measles in the legacy format is the percent of subjects with a negative baseline measles antibody titer, as defined by the optical density (OD) cutoff, with a postvaccination measles antibody titer ≥ 207.5 mIU/mL.

Samples from Protocols 009 and 011 were assayed in the legacy format Rubella ELISA, which reported antibody titers in Rubella ELISA units. To convert titers from ELISA units to IU/mL, titers for these 2 protocols were divided by 1.28.

ProQuad[®] (Middle Dose) = ProQuad[®] containing a varicella virus dose of $3.97 \log_{10}$ PFU.

ProQuad[®] (High Dose) = ProQuad[®] containing a varicella virus dose of $4.25 \log_{10}$ PFU.

ELISA = Enzyme-linked immunosorbent assay.

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

N = Number vaccinated at baseline.

n = Number of subjects who were per-protocol Postdose 1 and Postdose 2 and satisfied the given prevaccination serostatus cutoff.

CI = Confidence interval.

GMT = Geometric mean titer.

PFU = Plaque-forming units.

Immunogenicity in Children 4 to 6 Years of Age Who Received a First Dose of ProQuad[®] After Primary Vaccination With M-M-R[®] II and VARIVAX[®]

In a clinical trial, 799 healthy 4- to 6-year-old children who had received M-M-R[®] II and VARIVAX[®] at least 1 month prior to study entry were randomized to receive ProQuad[®] and placebo (N=399), M-M-R[®] II and placebo concomitantly at separate injection sites (N=205), or M-M-R[®] II and VARIVAX[®] concomitantly at separate injection sites (N=195). Children were eligible if they were previously administered primary doses of M-M-R[®] II and VARIVAX[®], either concomitantly or non-concomitantly, at 12 months of age or older. Children were excluded if they were recently exposed to measles, mumps, rubella, and/or varicella, had an immune impairment, or had a history of allergy to components of the vaccine(s). No concomitant vaccines were permitted during study participation (see ADVERSE REACTIONS for ethnicity and gender information).

A summary of antibody responses to measles, mumps, rubella, and varicella at 6 weeks postvaccination in subjects who had previously received M-M-R[®] II and VARIVAX[®] is shown in Table 7. Results from this study showed that a first dose of ProQuad[®] after primary vaccination with M-M-R[®] II and VARIVAX[®] elicited a positive antibody response to all four antigens in greater than 98% of subjects. Postvaccination GMTs for recipients of ProQuad[®] were similar to those following a second dose of M-M-R[®] II and VARIVAX[®] administered concomitantly at separate injection sites (the lower bound of the 95% CI around the fold difference in measles, mumps, rubella, and varicella GMTs excluded 0.5). Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of M-M-R[®] II given concomitantly with placebo (the lower bound of the 95% CI around the fold difference for the comparison of measles, mumps, and rubella GMTs excluded 0.5).

Table 7 – Summary of Antibody Responses to Measles, Mumps, Rubella, and Varicella at 6 Weeks Post-vaccination in Subjects 4 to 6 Years of Age Who Had Previously Received M-M-R[®] II and VARIVAX[®] (Per-Protocol Population)

Group Number (Description)	n	GMT (95% CI)	Seropositivity Rate (95% CI)	% ≥4-Fold Rise in Titer (95% CI)	Geometric Mean Fold Rise (95% CI)
Group 1 (N=399) (ProQuad [®] + placebo)	367	1985.9 (1817.6, 2169.9)	100% (99.0%, 100%)	4.9% (2.9%, 7.6%)	1.21 (1.13, 1.30)
Group 2 (N=205) (M-M-R [®] II + placebo)	185	2046.9 (1815.2, 2308.2)	100% (98.0%, 100%)	4.3% (1.9%, 8.3%)	1.28 (1.17, 1.40)
Group 3 (N=195) (M-M-R [®] II + VARIVAX [®])	171	2084.3 (1852.3, 2345.5)	99.4% (96.8%, 100%)	4.7% (2.0%, 9.0%)	1.31 (1.17, 1.46)
Mumps[‡]					
Group 1 (N=399) (ProQuad [®] + placebo)	367	206.0 (188.2, 225.4)	99.5% (98.0%, 99.9%)	27.2% (22.8%, 32.1%)	2.43 (2.19, 2.69)
Group 2 (N=205) (M-M-R [®] II + placebo)	185	308.5 (269.6, 352.9)	100% (98.0%, 100%)	41.1% (33.9%, 48.5%)	3.69 (3.14, 4.32)
Group 3 (N=195) (M-M-R [®] II + VARIVAX [®])	171	295.9 (262.5, 333.5)	100% (97.9%, 100%)	41.5% (34.0%, 49.3%)	3.36 (2.84, 3.97)
Rubella[§]					
Group 1 (N=399) (ProQuad [®] + placebo)	367	217.3 (200.1, 236.0)	100% (99.0%, 100%)	32.7% (27.9%, 37.8%)	3.00 (2.72, 3.31)
Group 2 (N=205) (M-M-R [®] II + placebo)	185	174.0 (157.3, 192.6)	100% (98.0%, 100%)	31.9% (25.2%, 39.1%)	2.81 (2.41, 3.27)
Group 3 (N=195) (M-M-R [®] II + VARIVAX [®])	171	154.1 (138.9, 170.9)	99.4% (96.8%, 100%)	26.9% (20.4%, 34.2%)	2.47 (2.17, 2.81)
Varicella[*]					
Group 1 (N=399) (ProQuad [®] + placebo)	367	322.2 (278.9, 372.2)	98.9% (97.2%, 99.7%)	80.7 (76.2%, 84.6%)	12.43 (10.63, 14.53)
Group 2 (N=205) (M-M-R [®] II + placebo)	185	N/A	N/A	N/A	N/A
Group 3 (N=195) (M-M-R [®] II + VARIVAX [®])	171	209.3 (171.2, 255.9)	99.4% (96.8%, 100%)	71.9% (64.6%, 78.5%)	8.50 (6.69, 10.81)
[†] Measles GMTs are reported in mIU/mL; seropositivity corresponds to ≥120 mIU/mL. [‡] Mumps GMTs are reported in mumps Ab units/mL; seropositivity corresponds to ≥10 Ab units/mL. [§] Rubella titers obtained by the legacy format were converted to their corresponding titers in the modified format. Rubella serostatus was determined after the conversion to IU/mL: seropositivity corresponds to ≥10 IU/mL. [*] Varicella GMTs are reported in gpELISA units/mL; seropositivity rate is reported by % of subjects with postvaccination antibody titers ≥5 gpELISA units/mL. Percentages are calculated as the number of subjects who met the criterion divided by the number of subjects contributing to the per-protocol analysis. gpELISA = Glycoprotein enzyme-linked immunosorbent assay; ELISA = Enzyme-linked immunosorbent assay; CI = Confidence interval; GMT = Geometric mean titer; N/A = Not applicable; N = Number of subjects vaccinated; n = number of subjects in the per-protocol analysis.					

Immunogenicity Following Concomitant Use with Other Vaccines ProQuad[®] with Pneumococcal 7-valent Conjugate Vaccine and/or VAQTA[®]

In a clinical trial, 1027 healthy children 12 to 15 months of age were randomized to receive ProQuad[®] and pneumococcal 7-valent conjugate vaccine concomitantly (N=510) at separate injection sites or ProQuad[®] and pneumococcal 7-valent conjugate vaccine non-concomitantly (N=517) at separate clinic visits (see ADVERSE REACTIONS for ethnicity and gender information). The statistical analysis of non-inferiority in antibody response rates to measles, mumps, rubella, and varicella at 6 weeks postvaccination for subjects are shown in Table 8. In the per-protocol population, seroconversion rates were not inferior in children given ProQuad[®] and pneumococcal 7-valent conjugate vaccine concomitantly when compared to seroconversion rates seen in children given these vaccines non-concomitantly for measles, mumps, and rubella. In children with baseline varicella antibody titers <1.25 gpELISA units/mL, the varicella seroprotection rates were not inferior when rates after concomitant and non-concomitant vaccination were compared 6 weeks postvaccination. Statistical analysis of non-inferiority in GMTs to *S. pneumoniae* serotypes at 6 weeks postvaccination are shown in Table 9. Geometric mean antibody titers (GMTs) for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were not inferior when antibody titers in the concomitant and non-concomitant groups were compared 6 weeks postvaccination.

Table 8 – Statistical Analysis of Non-Inferiority in Antibody Response Rates to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella, or With Varicella Antibody Titer <1.25 gpELISA units at Baseline in the ProQuad® + PCV7* Treatment Group and the ProQuad® followed by PCV7 Control Group (Per-Protocol Analysis)

Assay Parameter	ProQuad® + PCV7 (N=510)		ProQuad® followed by PCV7 (N=259)		Difference (percentage points) ^{a,b} (95% CI)
	n	Estimated Response ^a	n	Estimated Response ^a	
Measles % ≥255 mIU/mL	406	97.3%	204	99.5%	-2.2 (-4.6, 0.2)
Mumps % ≥10 Ab units/mL	403	96.6%	208	98.6%	-1.9 (-4.5, 1.0)
Rubella % ≥10 IU/mL	377	98.7%	195	97.9%	0.9 (-1.3, 4.1)
Varicella % ≥5 gpELISA units/mL	379	92.5%	192	87.9%	4.5 (-0.4, 10.4)

* PCV7 = Pneumococcal 7-valent conjugate vaccine. Seronegative defined as baseline measles antibody titer <255 mIU/mL for measles, baseline mumps antibody titer <10 ELISA Ab units/mL for mumps, and baseline rubella antibody titer <10 IU/mL for rubella.

^a Estimated responses and their differences were based on statistical analysis models adjusting for study center.

^b ProQuad® + PCV7 - ProQuad® followed by PCV7.

The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -10 percentage points (*i.e.* excluding a decrease equal to or more than the prespecified criterion of 10.0 percentage points). This indicates that the difference is statistically significantly less than the prespecified clinically relevant decrease of 10.0 percentage points at the 1-sided alpha = 0.025 level.

N = Number of subjects vaccinated in each treatment group;

n = Number of subjects with measles antibody titer <255 mIU/mL, mumps antibody titer <10 ELISA Ab units/mL, rubella antibody titer <10 IU/mL, or varicella antibody titer <1.25 gpELISA units/mL at baseline and with post-vaccination serology contributing to the per-protocol analysis;

Ab = antibody;

ELISA = Enzyme-linked immunosorbent assay;

gpELISA = Glycoprotein enzyme-linked immunosorbent assay;

CI = Confidence interval.

Table 9 – Statistical Analysis of Non-Inferiority in GMTs to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination in the ProQuad® + PCV7* Treatment Group and the PCV7 Followed by ProQuad® Control Group (Per-Protocol Analysis)

Serotype	Parameter	Group 1 ProQuad® + PCV7 (N=510)		Group 2 PCV7 followed by ProQuad® (N=258)		Fold-Difference ^{b,*} (95% CI)
		n	Estimated Response ^a	n	Estimated Response ^a	
4	GMT	410	1.5	193	1.3	1.2 (1.0, 1.4)
6B	GMT	410	8.9	192	8.4	1.1 (0.9, 1.2)
9V	GMT	409	2.9	193	2.5	1.2 (1.0, 1.3)
14	GMT	408	6.5	193	5.7	1.1 (1.0, 1.3)
18C	GMT	408	2.3	193	2.0	1.2 (1.0, 1.3)
19F	GMT	408	3.5	192	3.1	1.1 (1.0, 1.3)
23F	GMT	413	4.1	197	3.7	1.1 (1.0, 1.3)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.

^a Estimated responses and their fold-difference were based on statistical analysis models adjusting for study center and prevaccination titer.

^b ProQuad® + PCV7 / PCV7 followed by ProQuad®.

The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5, (*i.e.* excluding a decrease of 2-fold or more). This indicates that the fold-difference is statistically significantly less than the pre-specified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.

N = Number of subjects vaccinated in each treatment group;

n = Number of subjects contributing to the per-protocol analysis for the given serotype;

GMT = geometric mean titer;

CI = Confidence interval.

In a clinical trial, 653 healthy children 12 to 15 months of age were randomized to receive VAQTA®, ProQuad®, and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or ProQuad® and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA® 6 weeks later (N=323) [see ADVERSE REACTIONS for ethnicity and gender information]. Statistical analysis of non-inferiority of the response rate for varicella antibody at 6 weeks postvaccination among subjects who received VAQTA® concomitantly or non-concomitantly with ProQuad® and pneumococcal 7-valent conjugate vaccine is shown in Table 10. For the varicella component of ProQuad®, in subjects with baseline antibody titers <1.25 gpELISA units/mL, the proportion with a titer ≥5 gpELISA units/mL 6 weeks after their first dose of ProQuad® was non-inferior when ProQuad® was administered with VAQTA® and pneumococcal 7-valent conjugate vaccine as compared to the proportion with a titer ≥5 gpELISA units/mL when ProQuad® was administered with pneumococcal 7-valent conjugate vaccine alone. Statistical analysis of non-inferiority of the seropositivity rate for hepatitis A antibody at 4 weeks postdose 2 of VAQTA® among subjects who received VAQTA® concomitantly or non-concomitantly with ProQuad® and pneumococcal 7-valent conjugate vaccine is shown in Table 11. The seropositivity rate to hepatitis A 4 weeks after a second dose of VAQTA® given concomitantly with ProQuad® and pneumococcal 7-valent conjugate vaccine (defined as the percent of subjects with a titer ≥10 mIU/mL) was non-inferior to the seropositivity rate observed when VAQTA® was administered separately from ProQuad® and pneumococcal 7-valent conjugate vaccine. Statistical analysis of non-inferiority in GMT to *S. pneumoniae* serotypes at 6 weeks postvaccination among subjects who received VAQTA® concomitantly or non-concomitantly with ProQuad® and pneumococcal 7-valent conjugate vaccine is shown in Table 12. Additionally, the GMTs for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after vaccination with pneumococcal 7-valent conjugate vaccine administered concomitantly with ProQuad® and VAQTA® were non-inferior as compared to GMTs observed in the group given pneumococcal 7-valent

conjugate vaccine with ProQuad[®] alone. An earlier clinical study involving 617 healthy children provided data that indicated that the seroresponse rates 6 weeks post vaccination for measles, mumps, and rubella in those given M-M-R[®] II and VAQTA[®] concomitantly (N=309) were non-inferior as compared to historical controls.

Table 10– Statistical Analysis of Non-Inferiority of the Response Rate for Varicella Antibody at 6 Weeks Postvaccination Among Subjects Who Received VAQTA[®] Concomitantly or Non-Concomitantly With ProQuad[®] and PCV7* (Per-Protocol Analysis Set)

	Group 1: Concomitant VAQTA[®] with ProQuad[®] + PCV7 (N=330)		Group 2: Non-concomitant VAQTA[®] separate from ProQuad[®] + PCV7 (N=323)		Difference^a (percentage points): Group 1 – Group 2 (95% CI)
Parameter	n	Estimated Response^a	n	Estimated Response^a	
% ≥5 gpELISA units/mL ^b	225 ^c	93.2%	232 ^c	98.3%	-5.1 (-9.3, -1.4)
<p>*PCV7 = Pneumococcal 7-valent conjugate vaccine N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per protocol analysis for varicella; CI = Confidence interval. ^a Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center. ^b 6 weeks following Dose 1. ^c Initial Serostatus <1.25 gpELISA units/ mL. The conclusion of similarity (non-inferiority) was based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease of 10 percentage points or more (lower bound >-10.0). This indicated that the risk difference was statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.</p>					

Table 11 – Statistical Analysis of Non-Inferiority of the Seropositivity Rate (SPR) for Hepatitis A Antibody at 4 Weeks Postdose 2 of VAQTA® Among Subjects Who Received VAQTA® Concomitantly or Non-Concomitantly With ProQuad® and PCV7* (Per-Protocol Analysis Set)

	Group 1: Concomitant VAQTA® with ProQuad® + PCV7 (N=330)		Group 2: Non-concomitant VAQTA® separate from ProQuad® + PCV7 (N=323)		Difference ^a (percentage points): Group 1 - Group 2 (95% CI)
Parameter	n	Estimated Response ^a	n	Estimated Response ^a	
% ≥10 mIU/mL ^b	182 ^c	100.0%	159 ^c	99.3%	0.7 (-1.4, 3.8)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
 CI = Confidence interval; N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for hepatitis A.
^a Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.
^b 4 weeks following receipt of 2 doses of VAQTA®.
^c Regardless of initial serostatus.
 The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -10 percentage points (*i.e.* excluding a decrease of 10 percentage points or more) [lower bound >-10.0]. This indicated that the risk difference was statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.

Table 12 – Statistical Analysis of Non-Inferiority in Geometric Mean Titers (GMT) to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination Among Subjects Who Received VAQTA® Concomitantly or Non-Concomitantly With ProQuad® and PCV7* (Per-Protocol Analysis Set)

	Group 1: Concomitant VAQTA® with ProQuad® + PCV7 (N=330)		Group 2: Non-concomitant VAQTA® separate from ProQuad® + PCV7 (N=323)		
Serotype	n	Estimated Response ^a	n	Estimated Response ^a	Fold-Difference ^a (95% CI)
4	246	1.9	247	1.7	1.1 (0.9, 1.3)
6B	246	9.9	246	9.9	1.0 (0.8, 1.2)
9V	247	3.7	247	4.2	0.9 (0.8, 1.0)
14	248	7.8	247	7.6	1.0 (0.9, 1.2)
18C	247	2.9	247	2.7	1.1 (0.9, 1.3)
19F	248	4.0	248	3.8	1.1 (0.9, 1.2)
23F	247	5.1	247	4.4	1.1 (1.0, 1.3)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
 CI = Confidence interval; GMT = Geometric mean titer; N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for *S. pneumoniae* serotypes.
^a Estimated responses and their fold-difference were based on statistical analysis models adjusting for combined study center and prevaccination titer.
 The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5 (*i.e.* excluding a decrease of 2-fold or more). This indicates that the fold-difference was statistically significantly less than the prespecified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.

ProQuad[®] Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine

In a clinical trial, 1913 healthy children 12 to 15 months of age were randomized to receive ProQuad[®] plus diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine concomitantly at separate injection sites (N=949), ProQuad[®] at the initial visit followed by DTaP and *Haemophilus* b conjugate and hepatitis B (recombinant) vaccine given concomitantly 6 weeks later (N=485), or M-M-R[®] II and VARIVAX[®] given concomitantly at separate injection sites (N=479) at the first visit (see ADVERSE REACTIONS for ethnicity and gender information). Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, anti-PRP, and hepatitis B were comparable between the 2 groups given ProQuad[®] at approximately 6 weeks postvaccination indicating that ProQuad[®] and *Haemophilus* b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine may be administered concomitantly at separate injection sites (see Table 13 below). Response rates for measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, and hepatitis B were not inferior in children given ProQuad[®] plus *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines concomitantly when compared to ProQuad[®] at the initial visit and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines given concomitantly, 6 weeks later. There are insufficient data to support concomitant vaccination with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (data not shown).

Table 13 – Summary of the Comparison of the Immunogenicity Endpoints for Measles, Mumps, Rubella, Varicella, *Haemophilus influenzae* type b, and Hepatitis B Responses Following Vaccination with ProQuad[®], *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant) Vaccine and DTaP Administered Concomitantly Versus Non-Concomitant Vaccination with ProQuad[®] Followed by These Vaccines

Vaccine Antigen	Parameter	Concomitant Group	Non-Concomitant Group	Risk Difference (95% CI)	Criterion for Non-inferiority
		N=949	N=485		
		Response	Response		
Measles	% ≥120 mIU/mL	97.8%	98.7%	-0.9 (-2.3, 0.6)	LB >-5.0
Mumps	% ≥10 ELISA Ab units/mL	95.4%	95.1%	0.3 (-1.7, 2.6)	LB >-5.0
Rubella	% ≥10 IU/mL	98.6%	99.3%	-0.7 (-1.8, 0.5)	LB >-5.0
Varicella	% ≥5 gpELISA units/mL	89.6%	90.8%	-1.2 (-4.1, 2.0)	LB >-10.0
HiB-PRP	% ≥1.0 mcg/mL	94.6%	96.5%	-1.9 (-4.1, 0.8)	LB >-10.0
HepB	% ≥10 mIU/mL	95.9%	98.8%	-2.8 (-4.8, -0.8)	LB >10.0
HiB-PRP = <i>Haemophilus influenzae</i> type b, polyribosyl phosphate; HepB = hepatitis B; LB = lower bound, limit for non-inferiority comparison.					

Persistence of Immune Response

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2107 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.¹⁵ 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.

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PART III: CONSUMER INFORMATION**ProQuad®****Measles, Mumps, Rubella and Varicella
Virus Vaccine Live**

This leaflet is part III of a three-part “Product Monograph” published when ProQuad® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ProQuad®. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE**What the vaccine is used for:**

ProQuad® is an injectable live, attenuated virus vaccine to help prevent measles (rubeola), mumps, rubella (German measles), and varicella (chickenpox).

What it does:

The doctor has recommended or administered ProQuad® to help protect your child against measles, mumps, rubella, and varicella. The vaccine can be administered to persons 12 months through 12 years of age.

Measles (rubeola) is a serious infectious illness that is very easily passed from one person to another. It causes a high fever, cough, and a rash and lasts for 1 to 2 weeks. One out of every 10 children who catch measles will also have an ear infection or pneumonia. On rare occasions, measles can also cause an infection of the brain that could lead to seizures, hearing loss, mental retardation, and even death. Babies and adults who catch measles are often much sicker for a longer time or are more likely to die than elementary school children and teenagers who catch measles.

Mumps is an infectious illness that is easily passed from one person to another and causes fever, headache, and swollen, painful glands under the jaw (salivary glands). It can sometimes be a very serious disease and usually lasts for several days. Mumps can cause a mild inflammation of the coverings of the brain and spinal cord (meningitis) in about 1 person in every 10 who catch it. About 1 out of every 4 teenage or adult males with mumps will have a painful swelling of the testicles for several days (this does not usually affect their ability to father children). Teenagers and adults, especially males, who catch mumps are often much sicker and more likely to suffer longer than children do.

Rubella (German measles) is usually a mild disease that causes a mild fever, swollen glands in the neck, pain and swelling in the joints, and a rash that lasts for a short time **but is very dangerous if a pregnant woman catches it**. Women who catch rubella when they are pregnant can have babies who are stillborn, or have heart disease, blindness, deafness, or problems with learning.

Varicella (chickenpox) is an infectious illness that is easily passed from one person to another and occurs most often in children 5 to 9 years of age. It is primarily spread from person to person through the air by sneezing or coughing. Symptoms of varicella

include mild headache, moderate fever, and general discomfort. These are followed by a rash of itchy, little red spots which usually start on the chest, stomach or back, but can appear anywhere on the body. There may be only a few spots or clusters of spots, or even hundreds of spots that develop over the next 3 to 5 days. The spots will change into clear blisters filled with fluid which then become cloudy, break open, dry, scab, and heal, usually within 5 to 20 days. The most common complications are bacterial skin infections. Less frequent but very serious complications include pneumonia, inflammation of the brain (encephalitis), Reye Syndrome (inflammation of the liver associated with disturbances of consciousness), and death. Severe disease and serious complications are more likely to occur in adolescents and adults. Disease and accompanying complications from varicella have significantly fallen since the introduction of a varicella vaccine in 1995.

What the medicinal ingredient is:

The medicinal ingredient is an injectable live attenuated virus vaccine to help prevent measles (rubeola), mumps, rubella (German measles), and varicella (chickenpox).

What the important nonmedicinal ingredients are:

ProQuad® contains gelatine, human albumin and a trace amount of neomycin as inactive ingredients. Tell the doctor if your child has ever had an allergic reaction to these ingredients.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

WARNINGS AND PRECAUTIONS**When it should not be used:**

ProQuad® should not be used if the vaccine recipient:

- is allergic to any of its components (including neomycin and gelatin)
- has a blood disorder or any type of cancer that affects the immune system (other than corticosteroid replacement)
- is taking medications to suppress the immune system (other than corticosteroid replacement)
- has an immune deficiency as a result of a disease (such as AIDS) or a treatment
- has active untreated tuberculosis
- has a fever higher than 38.5 °C; however, low-grade fever itself is not a reason to delay vaccination
- is pregnant (in addition, pregnancy should be avoided for 3 months after vaccination)

What should the doctor be told before my child is vaccinated with ProQuad®?

Tell the doctor about any medical problems your child has or has had, and about any allergies (especially to neomycin).

Tell the doctor if your child has a history of seizures or a brain injury, a low blood platelet count, or has received blood or plasma transfusions or administration of human serum globulin within the last 5 months.

The Oka/Merck strain of varicella virus has been shown to be transmitted from recipients of varicella vaccine to people at risk

of catching varicella, although this has occurred rarely. This strain of varicella virus is in ProQuad[®]. Whenever possible, individuals who have been vaccinated with ProQuad[®] should attempt to avoid contact, for up to 6 weeks following the vaccination, with people for whom the disease may be particularly serious. These individuals include:

- individuals with a weakened immune system
- pregnant women who never had varicella
- newborn babies whose mothers never had varicella

Tell the doctor if there is anyone who falls into one of the categories above and is expected to be in contact with the vaccine recipient.

ProQuad[®] may be used for vaccination against measles, mumps, rubella, and varicella. The appropriate time and number of injections will be determined by your doctor using appropriate official recommendations.

Use in pregnancy

ProQuad[®] should not be administered to pregnant women. Women of child-bearing age should take the necessary precautions to avoid pregnancy for 3 months following vaccination.

Use in breast-feeding

Tell the doctor if the vaccine recipient is breast-feeding or intends to breast-feed. Your doctor will decide if ProQuad[®] should be given.

INTERACTIONS WITH THIS VACCINE

Can my child be vaccinated with ProQuad[®] and other vaccines at the same time?

Tell the doctor if your child has recently received a vaccine or if one is scheduled to be given in the near future. The doctor will determine when ProQuad[®] may be given. At least 1 month should elapse between a dose of measles, mumps, and rubella vaccine and ProQuad[®]. If for any reason a second dose of a varicella-containing vaccine is required, at least 1 month should elapse between administration of the doses.

The doctor may delay vaccination for 3 or more months following blood or plasma transfusions, or administration of normal human immune globulin (IG), or varicella zoster immune globulin (VZIG).

Can my child have medical tests with ProQuad[®]?

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

Can my child be vaccinated with ProQuad[®] and receive other medicines at the same time?

The use of salicylates (for example, acetylsalicylic acid or aspirin) should be avoided for 6 weeks following vaccination with ProQuad[®] because the use of salicylates during natural varicella infection has been associated with Reye Syndrome (see ABOUT THIS VACCINE, What it does)

PROPER USE OF THIS VACCINE

What is the vaccination schedule for ProQuad[®]?

ProQuad[®] is given by subcutaneous injection to persons 12 months through 12 years of age. If a second dose of a measles-containing vaccine is needed, then ProQuad[®] can be used for this dose. The appropriate time and number of injections will be determined by your doctor using appropriate official recommendations.

Talk to the doctor for more details.

Overdose:

There are no data with regard to overdose.

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Your doctor will decide when to give the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What undesirable effects may ProQuad[®] have?

Like all vaccines, ProQuad[®] can have side effects.

The most common side effects reported with the use of ProQuad[®] were: injection-site complaints including pain/tenderness/soreness, redness, swelling or bruising; fever (38.9 °C or higher); irritability; rash (including measles-like rash, varicella-like rash, viral exanthema, and injection-site rash); upper respiratory infection; vomiting and diarrhea.

Other less common side effects have been reported following administration of ProQuad[®], and some of these were serious. These included: allergic reactions (hives); seizures with a fever; cough and bronchiolitis; and unsteadiness with walking.

Other adverse events have been reported with the use of at least one of the following: ProQuad[®], M-M-R[®] II (measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.), the monovalent components of M-M-R[®] II, or VARIVAX[®] (varicella virus vaccine, live, attenuated, [Oka/Merck]). These adverse events include bruising more easily than normal; red or purple, flat, pinhead spots under the skin; severe paleness; unusual bleeding or bruising under the skin; swelling of the testicles; tingling of the skin; herpes zoster (shingles); inflammation of the brain and spinal cord (encephalitis and acute disseminated encephalomyelitis); severe skin disorders; skin infection; stroke; seizures without a fever; joint pain and/or swelling (which could be transient or chronic); inflammation of the lung (pneumonia/pneumonitis); and varicella (chickenpox).

The doctor has a more complete list of side effects for ProQuad[®] and for the vaccine components for ProQuad[®] (M-M-R[®] II and VARIVAX[®]).

Tell the doctor promptly about any of these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

Reporting Suspected Vaccine Adverse Events

For the general public:

If you suspect you have had a serious or unexpected event following receipt of a vaccine, please ask your healthcare professional to complete the Adverse Events Following Immunization (AEFI) Form and send it to your local [health unit](#) in your province/territory.

For healthcare professionals:

If a patient experiences an adverse event following immunization, please complete the Adverse Events Following Immunization (AEFI) Form and send it to your local [health unit](#) in your province/territory.

If you have any questions or have difficulty contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

Toll-free telephone: 1-866-844-0018

Toll-free fax: 1-866-844-5931

By email: caefi@phac-aspc.gc.ca

NOTE: Should you require information related to the management of the adverse events, please contact your health professional before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

If you want more information about ProQuad®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or Merck Canada website www.merck.ca or by calling Merck Canada at 1 800-567-2594

To report an adverse event related to ProQuad®, please contact 1-800-567-2594.

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