Product Monograph

Including Patient Medication Information

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
ATC code: J07BD54

Merck Canada Inc.
16750 route Transcanadienne
Kirkland QC Canada H9H 4M7
www.merck.ca

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Recent Major Label Changes

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Part 1: Health Professional Information

1 Indications

ProQuad® (measles, mumps, rubella and varicella virus vaccine live) is a vaccine indicated for the prevention of measles, mumps, rubella, and varicella in children 12 months through 6 years of age.

1.1 Pediatrics

Pediatrics (<1 year): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatrics less than 1 year of age.

Pediatrics (6-12 years): 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®.

1.2 Geriatrics (≥ Age 65)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 Contraindications

- History of hypersensitivity to any component of the vaccine, including gelatin. For a complete listing, see 6 Dosage Forms, Strengths, 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.
- Do not give ProQuad® to pregnant females. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination (see 7.1.1 Pregnancy).

4 Dosage and Administration

4.1 Dosing Considerations

- Individuals 12 months through 12 years of age should receive a single dose of ProQuad® administered intramuscularly or subcutaneously. This 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 containing vaccine is needed, ProQuad® may be used for this second dose. The second dose can be administered from 18 months of age or anytime thereafter, 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 3 months should elapse between a dose of varicella-containing vaccine and ProQuad®.

- Refer to the most current Canadian Immunization recommendations.[1]

- Do not give immune globulin (Ig) or Varicella Zoster Immune Globulin (VZIG) concomitantly with ProQuad® (see 9 Drug Interactions).

4.2 Recommended Dose and Dosage Adjustment

Each 0.5-mL dose contains not less than 3.00 $\log_{10}$ $TCID_{50}$ (50% tissue culture infectious dose) of measles virus; 4.30 $\log_{10}$ $TCID_{50}$ of mumps virus; 3.00 $\log_{10}$ $TCID_{50}$ of rubella virus; and a minimum of 3.99 $\log_{10}$ PFU (plaque-forming units) of Oka/Merck varicella virus.

4.3 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.

[1] Canadian Immunization Guide: Part 4. Immunizing agents - Canada.ca

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 1 – Reconstitution of ProQuad®

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

4.4 Administration

FOR INTRAMUSCULAR OR 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 9 Drug Interactions).

5 Overdose

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

For the most recent information in the management of a suspected vaccine overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 2 – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Intramuscular or subcutaneous injection	Lyophilized powder for injection Each 0.5 mL dose contains Immunogens: Measles ≥ 3.00 $\log_{10}$ $TCID_{50}$ (50% tissue culture infectious dose) Mumps ≥ 4.30 $\log_{10}$ $TCID_{50}$ Rubella ≥ 3.00 $\log_{10}$ $TCID_{50}$ Varicella ≥ 3.99 $\log_{10}$ PFU	Bovine serum albumin Buffer and media ingredients Hydrolyzed gelatin Monosodium L-glutamate MRC-5 cell residuals Neomycin Potassium chloride Potassium Phosphate Recombinant human albumin (rHA) Sodium bicarbonate Sodium chloride Sodium phosphate Sorbitol Sucrose Urea

Description

ProQuad® is supplied as follows:

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

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.

7 Warnings and Precautions

General

Administer ProQuad® intramuscularly or subcutaneously; do not give it 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 8 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 8 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 2 Contraindications).

The duration of protection from measles, mumps, rubella, and varicella infection after vaccination with ProQuad® is unknown (see 10 Clinical Pharmacology).

As for any vaccine, vaccination with ProQuad® may not result in protection in all vaccine recipients.

Adolescents and Adults

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

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 8 Adverse Reactions).

Monitoring and Laboratory Tests

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®.

Albumin

This product contains albumin, a derivative of human blood. Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), no cases of transmission of CJD or viral diseases have ever been identified that were associated with the use of albumin.

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 to reduce the risk of getting measles and varicella with a measles-containing vaccine and varicella-containing vaccine, respectively, when administered to the susceptible individuals within 3 days of exposure.

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.

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 7.1.2 Breastfeeding).

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

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

High-risk individuals susceptible to varicella include:

- Immunocompromised individuals (see 2 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.

Tuberculosis

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

Reproductive Health: Female and Male Potential

In females of childbearing age, pregnancy should be avoided for 3 months following vaccination (see 7.1.1 Pregnancy).

- **Fertility**

ProQuad® has not been evaluated for its potential to impair fertility.

- **Teratogenic Risk**

The possible effects of the vaccine on fetal development are unknown.

7.1 Special Populations

7.1.1 Pregnancy

Studies have not been conducted with ProQuad® in pregnant women. ProQuad® should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see 1 Indications and 2 Contraindications).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) Reports have indicated that contracting wild-type measles during pregnancy enhances 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) Wild-type rubella infection during pregnancy, especially in the first trimester, can lead to miscarriage, stillbirth, or Congenital Rubella Syndrome (CRS). In an 18-year survey involving over 1200 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 683 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with CSR. Subsequent post-marketing surveillance has identified CRS associated with a rubella vaccine strain following inadvertent vaccination of a pregnant female with a measles, mumps, and rubella vaccine; and (4) Wild-type varicella can sometimes cause harm to the fetus.

7.1.2 Breastfeeding

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.

7.1.3 Pediatrics

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.

7.1.4 Geriatrics

ProQuad® is not indicated for use in the geriatric population.

8 Adverse Reactions

8.1 Adverse Reaction Overview

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 unsteadiness with walking.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Children 12 through 23 months of age

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

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

The only systemic vaccine-related adverse experiences that were reported at a significantly greater rate in individuals who received ProQuad® than in individuals who received M-M-R® II and VARIVAX® concomitantly at separate injection sites were fever (≥38.9 °C 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).

Table 3 summarizes the frequencies of injection-site and systemic adverse experiences that were reported as vaccine-related by the investigator among ≥1% of children in these clinical trials.

Table 3 - Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children who received 1 Dose of ProQuad® or M-M-R® II and VARIVAX® at 12 to 23 months of Age (0 to 42 Days Postvaccination)

	ProQuad® (frozen) N=4497 n=4424 (%)	**M-M-R® II and VARIVAX® N=2038 n=1997 (%)**
Injection site*		
Pain/tenderness/soreness†	22.0	26.7
Erythema†	14.4	15.8
Swelling†	8.4	9.8
Ecchymosis	1.5	2.3
Rash	2.3	1.5
Systemic		
Fever†,‡	21.5	14.9
Irritability	6.7	6.7
Measles-like rash†	3.0	2.1
Varicella-like rash†	2.1	2.2
Rash (not otherwise specified)	1.6	1.4
Upper respiratory infection	1.3	1.1
Viral exanthema	1.2	1.1
Diarrhea	1.2	1.3

*Injection-site adverse reactions for M-M-R® II and VARIVAX® are based on occurrence with either of the vaccines administered.

† Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 0 to 4 postvaccination.

‡ Temperature reported as elevated (≥102°F (≥38.8°C), oral equivalent) or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

Injection-site and systemic adverse reactions observed among recipients of ProQuad® refrigerator-stable and ProQuad® Frozen at a rate of at least 1% are shown in Table 4.

Table 4 - Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad® Refrigerator-Stable and ProQuad® Frozen at 12 to 23 Months of Age (0 to 42 Days Postvaccination)

Adverse Reactions	ProQuad (refrigerator-stable) (N=1006) (n=983) %	ProQuad (frozen) (N=513) (n=500) %
Injection Site		
Pain/tenderness/soreness*	29.6	30.4
Erythema*	17.8	18.0
Swelling*	8.7	9.2
Hemorrhage	1.5	1.2
Systemic		
Fever*,†	10.6	9.0
Irritability	4.9	6.6
Measles-like rash*	4.9	6.0
Varicella-like rash*	3.0	1.8
Upper respiratory infection	1.7	1.4
Vomiting	1.4	1.4
Diarrhea	1.3	0.8
Nasopharyngitis	1.2	0.8
Eczema	1.0	1.2

* Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.

† Temperature reported as elevated (≥102°F (≥38.8°C), oral equivalent) or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

In a randomized open-label clinical trial, conducted in France, 405 children 12 months through 18 months of age received 2 doses of ProQuad, administered 30 days apart, (an interval not approved in Canada) by either the intramuscular (n=202) or subcutaneous (n=203) route. In the overall population, 50.9% were male and the median age was 13.3 months. Local and systemic solicited adverse reactions were recorded by parents or guardians using standardized diary cards. Local solicited reactions were recorded for 4 days after vaccination, and systemic solicited adverse reactions were recorded for 28 days after vaccination. In the event that a participant experienced a rash or a mumps-like illness, parents and/or guardians were instructed to contact the investigator for an examination as soon as possible and no later than 72 hours following onset of symptoms. The

nature of any rash was characterized by the principal investigator either as measles-like, rubella-like, varicella-like or "other". Study investigators reviewed the diary card with the participant or participant's legal guardian 30 days and 42 days after dose 1 and dose 2, respectively to ensure consistency with protocol definitions. Tables 5 and 6 below present the frequency of solicited adverse reactions based on the final assessment by the study investigators.

Table 5: Proportion of Participants Reporting Solicited Adverse Reactions Following First Vaccination with ProQuad, by the Intramuscular or Subcutaneous Route

	INTRAMUSCULAR N=202 %	SUBCUTANEOUS N=203 %
Solicited local reactions at ProQuad injection site (Days 0 to 4)*		
Erythema[†]	5.0	14.3
Mild	4.5	12.8
Moderate	0	1.5
Severe	0	0
Missing	0.5	0
Pain[‡]	10.9	5.9
Mild	8.9	3.9
Moderate	2.0	2.0
Severe	0	0
Swelling[†]	1.0	3.9
Mild	1.0	3.9
Moderate	0	0
Severe	0	0
Solicited systemic reactions (Days 0 to 28)		
Measles-like rash	0.5	2.0
Rubella-like rash	3.0	3.0
Varicella-like rash	1.0	0.5
Zoster-like rash	0	0
Mumps-like illness	0.5	0
Fever (temperature ≥38.0°C)[§,¶]	62.8	68.3
38.0-38.5°C	21.1	17.6
>38.5-39.0°C	18.1	21.6
>39.0-39.5°C	14.1	18.1
>39.5-40.0°C	7.0	9.0
>40.0°C	2.5	2.0

N=total number of participants in the group
* Post-dose 1 (0-28 days), there was one injection-site rubella-like rash and one injection-site varicella-like rash, and both were reported in the subcutaneous group.
† Intensity of injection site reaction: mild or ≤2.5 cm; moderate or >2.5 to ≤5.0 cm; severe or >5.0 cm.
‡ Intensity of pain: mild: awareness of symptom but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.
§ The percentage of fever is defined within the population who had valid temperature measurements. Three participants in IM group and four participants in SC group did not have temperature measurements and were excluded from the denominator; resulting in N=199 and N=199, respectively.
¶ In the IM Group 96.0% of fevers were documented using the rectal route of measurement and 4.0% of fevers were documented only by the axillary route of measurement. In the SC Group 99.3% of fevers were documented using the rectal route of measurement and 0.7% of fevers were documented only by the axillary route of measurement.

Table 6: Proportion of Participants Reporting Solicited Adverse Reactions Following Second Vaccination with ProQuad, by the Intramuscular or Subcutaneous Route

	INTRAMUSCULAR N=201 %	**SUBCUTANEOUS N=200 %**
Solicited injection-site adverse reactions (Days 0 to 4)*		
Erythema†	15.4	27.0
Mild	13.9	22.5
Moderate	1.0	4.5
Severe	0	0
Missing	0.5	0
Pain‡	10.0	10.0
Mild	9.0	7.0
Moderate	0.5	3.0
Severe	05	0
Swelling†	6.0	12.5
Mild	5.0	11.0
Moderate	1.0	1.0
Severe	0	0
Missing	0	0.5
Solicited systemic adverse reactions (Days 0 to 28)		
Measles-like rash	0	1.0

Rubella-like rash	2.0% (4/201)	1.0
Varicella-like rash	0	2.0
Zoster-like rash	0	0
Mumps-like illness	0.5	0
Fever (temperature ≥38.0°C)[§,¶]	50.0	47.2
38.0-38.5°C	13.8	16.4
>38.5-39.0°C	18.4	10.8
>39.0-39.5°C	11.2	11.3
>39.5-40.0°C	5.6	7.2
>40.0°C	1.0	1.5

N=total number of participants in the group
* Post-dose 2 (0-28 days), there was one injection-site measle-like rash and this was reported in the subcutaneous group.
[†] Intensity of injection site reaction: mild or ≤2.5 cm; moderate or >2.5 to ≤5.0 cm; severe or >5.0 cm.
[‡] Intensity of pain: mild: awareness of symptom but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.
[§] The percentage of fever is defined within the population who had valid temperature measurements. Five participants in IM group and five participants in SC group did not have temperature measurements and were excluded from the denominator; resulting in N=196 and N=195, respectively.
[¶] In the IM Group 95.9% of fevers were documented using the rectal route of measurement and 4.1% of fevers were documented only by the axillary route of measurement. In the SC Group 98.9% of fevers were documented using the rectal route of measurement and 1.1% of fevers were documented only by the axillary route of measurement.

Serious adverse events (day 0 to last visit), recorded using diary cards supplemented by medical review, occurred at a rate of 1% and 0.5% in each group post-dose 1 and 2, respectively. None of these serious adverse events were considered related to the study vaccination.

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse reactions reported at a frequency of uncommon (≥1/1000, <1/100) and rare (≥1/10,000, <1/1000)] are listed below.

Blood and lymphatic disorders:

Rare: lymphadenopathy

Ear and labyrinth disorders:

Rare: ear pain

Gastrointestinal:

Rare: nausea

General disorders and administration site conditions:

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

Infections and infestations:

Uncommon: gastroenteritis, ear infection/otitis, otitis media, pharyngitis, viral infection, viral rash

Rare: tonsillitis, varicella, viral gastroenteritis

Injury and poisoning, and procedural complications:

Rare: contusion

Immune system disorders:

Rare: allergy/hypersensitivity

Metabolism and nutrition disorders:

Uncommon: anorexia, decreased appetite

Nervous system disorders:

Uncommon: febrile seizure, somnolence

Rare: ataxia, headache, lethargy

Ophthalmologic:

Rare: conjunctivitis, tearing, visual discomfort

Psychiatric:

Uncommon: crying, insomnia, sleep disorder

Rare: agitation, clinging

Respiratory, thoracic, and mediastinal disorders:

Uncommon: cough, nasal congestion, respiratory congestion, rhinorrhea

Rare: wheezing

Skin and subcutaneous tissue disorders:

Uncommon: dermatitis (including contact and atopic), erythema, rubella-like rash[†], urticaria,

Rare: drug eruption, exanthema

Vascular disorders:

Rare: flushing

8.5 Post-Market Adverse Reactions

Other Adverse Experiences

Additional 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, measles, orchitis, parotitis, respiratory infection, skin infection, varicella (vaccine strain)

Blood and the lymphatic system disorders:

Aplastic anemia, lymphadenitis, 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

Nervous system disorders:

Acute disseminated encephalomyelitis (ADEM), afebrile convulsions or seizures, aseptic meningitis (see below), Bell's palsy, cerebrovascular accident, dizziness, encephalitis[‡] (see below), encephalopathy (see below), Guillain-Barré syndrome, hypersomnia, measles inclusion body encephalitis (see 2 Contraindications), meningitis[‡], ocular palsies, paraesthesia, polyneuritis, polyneuropathy, subacute sclerosing panencephalitis (see below), syncope, transverse myelitis, tremor

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

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, pneumonitis (see 2 Contraindications), pneumonia, sinusitis, sneezing, sore throat

Gastrointestinal disorders:

Abdominal pain, hematochezia, mouth ulcer

Skin and subcutaneous tissue disorders:

Erythema multiforme, Henoch-Schönlein purpura, panniculitis, pruritus, purpura, skin induration, Stevens-Johnson syndrome, acute hemorrhagic edema of infancy, skin granuloma associated with vaccine derived rubella virus.

Musculoskeletal, connective tissue and bone disorders:

Arthritis and/or arthralgia (usually transient and rarely chronic [see below]), musculoskeletal pain, myalgia, swelling

General disorders and administration site conditions:

Injection site complaints (burning and/or stinging of short duration, edema/swelling, hive-like rash, hematoma, induration, lump, vesicles, wheal and flare), inflammation, papillitis, stiffness, varicella like rash, 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 2 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 2 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 7. 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 7 – 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.

9 Drug Interactions

9.2 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 3 month should elapse between administration of the 2 doses.

The data are not sufficient to support concomitant vaccination with diphtheria, tetanus and acellular pertussis vaccine (see 10 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.

9.4 Drug-Drug Interactions

Immune Globulins and Transfusions

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. The specific recommendations for intervals between administration of antibody containing products and live virus vaccines can be found in the Canadian Immunization Guide (Blood products, human immunoglobulin and timing of immunization: Canadian Immunization Guide.)

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

Corticosteroids and Immunosuppressive Drugs

ProQuad vaccine should not be administered to individuals receiving immunosuppressive therapy, including high dose corticosteroids. Vaccination with ProQuad vaccine can result in disseminated disease and extensive vaccine-associated rash in individuals on immunosuppressive drugs(see 2 Contraindications).

Salicylates

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 10 Clinical Pharmacology, Reye Syndrome).

9.7 Drug/Laboratory Test Interactions

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either any time before, simultaneously with, or at least 4 to 6 weeks after immunisation with ProQuad.

10 Clinical Pharmacology

10.1 Mechanism of Action

Formal studies to evaluate the efficacy of ProQuad® have not been performed. However, the efficacy of M-M-R® II and VARIVAX® has been demonstrated in numerous studies.

Efficacy of the measles, mumps, and rubella components of ProQuad® was previously established in a series of double-blind controlled field trials with the monovalent vaccines produced by Merck Sharp & Dohme LLC, 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. 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®.

Long-term estimated efficacy for the vaccine against all forms of varicella over 10 years was 94%. Antibody responses against varicella virus ≥5 units/mL in the glycoprotein enzyme-linked immunosorbent assay (gpELISA, a highly sensitive assay which is not commercially available) have been shown to be highly correlated with long-term protection.

Herpes Zoster

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

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

Post Exposure Prophylaxis

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

Reye Syndrome

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

Studies with Other Vaccines

In a clinical trial involving 1913 healthy subjects 12 through 15 months of age, 949 received ProQuad®, 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 14 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® subcutaneously and Prevnar* concomitantly at separate injection sites, and 517 were randomized to receive ProQuad® and Prevnar* non-concomitantly. Seroconversion rates and antibody

titers for measles, mumps, rubella, varicella, and *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were comparable in the concomitant and non-concomitant groups at 6 weeks post-vaccination indicating that ProQuad® and Prevnar* can be administered concomitantly at separate injection sites. No clinically significant differences in adverse events were reported between treatment groups.

In a clinical trial involving 1800 healthy children 12 to 23 months of age, 1453 were randomized to receive 2 doses of VAQTA®, and 347 were randomized to receive 2 doses of VAQTA® concomitantly with 2 doses ProQuad® subcutaneously 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 Prevnar* concomitantly, and 323 were randomized to receive ProQuad® and Prevnar* concomitantly followed by VAQTA® 6 weeks later. Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, and *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were comparable between the 2 groups at 6 weeks post-vaccination indicating that ProQuad®, VAQTA®, and Prevnar* can be administered concomitantly at separate injection sites.

The safety profile of VAQTA® administered concomitantly with ProQuad® and Prevnar* (Group 1) was generally comparable to that administered separately from ProQuad® and Prevnar * (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.

10.2 Pharmacodynamics

Pharmacotherapeutic group: Vaccines, Viral Vaccine; ATC code: J07BD54

10.3 Pharmacokinetics

Duration of Effect

The duration of protection from measles, mumps, rubella, and varicella infection after vaccination with ProQuad® is unknown (see 10 Clinical Pharmacology).

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.

11 Storage, Stability, and Disposal

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 should be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. Refrigeration of the diluent is not needed. Store at 2°C to 27°C. Do not freeze the diluent.

Reconstituted Solutions

To maintain the potency, it is imperative that only the STERILE DILUENT For Merck Sharp & Dohme LLC 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**.

12 Special Handling Instructions

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

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Proper name: ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live)

Immunogens: Each 0.5-mL dose contains not less than 3.00 $\log_{10}$ $TCID_{50}$ (50% tissue culture infectious dose) of measles virus; 4.30 $\log_{10}$ $TCID_{50}$ of mumps virus; 3.00 $\log_{10}$ $TCID_{50}$ of rubella virus; and a minimum of 3.99 $\log_{10}$ PFU (plaque-forming units) of Oka/Merck varicella virus.

Product Characteristics:

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.): a more attenuated line of measles virus , derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture;the JERYL LYNN® (B level) strain of mumps virus propagated in chick embryo cell culture; the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts; and (2) the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells (same varicella strain as in VARIVAX®).

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
[1]The measles virus is produced in chick embryo cell culture.
[2]The mumps virus is produced in chick embryo cell culture.
[3]The rubella virus is produced in WI-38 human diploid lung fibroblasts.
[4]The varicella virus is produced in human diploid cells (MRC-5).

14 Clinical Trials

14.1 Clinical Trial by Indication

Table 8 – 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
013	Open, randomized	Group 1 Dosage: 0.5 mL Route of administration: Subcutaneous (ProQuad®), Intramuscular (Comvax* and Tripedia*) Duration: ProQuad®, Comvax* and Tripedia* on Day 0 Group 2 Dosage: 0.5 mL	1915 total	12.4 months

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age
		Route of administration: Subcutaneous (ProQuad®), Intramuscular (Comvax* and Tripedia*) Duration: ProQuad® on Day 0, Comvax* and Tripedia* on Day 42 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		
014	Double-blind, randomized	Group 1 Dosage: 0.5 mL Route of administration: Subcutaneous Duration: ProQuad® and placebo on Day 0 Group 2 Dosage: 0.5 mL Route of administration: Subcutaneous Duration: M-M-R® II and placebo on Day 0 Group 3 Dosage: 0.5 mL Route of administration: Subcutaneous Duration: M-M-R® II and VARIVAX® on Day 0	800 total	4.3 years
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	1027 total	12.6 months

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age
		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		
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
067	Open, randomized	Dosage 0.5ml: 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. Group 2: was administered at 4 separate study visits. On Day 1, ProQuad® + Prevnar* were	653 total	12.4 months

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age
		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. Route of administration: Subcutaneous: ProQuad® Intramuscular: VAQTA® and Prevnar* Duration: as above		
V221-036	Open, randomized	Dosage 0.5mL: Group 1: First dose of ProQuad® administered by the intramuscular route at 12 to 18 months of age and second dose of ProQuad® administered by the intramuscular route 30 days later. Group 2: First dose of ProQuad® administered by the subcutaneous route at 12 to 18 months of age and second dose of ProQuad® administered by the subcutaneous route 30 days later. Route of administration: intramuscular or subcutaneous Duration: as above	405 total	13.7 months
‡ Subjects were blinded for the first dose only. § Subjects were blinded to the formulation of ProQuad® received.				

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 9. 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 9 – Summary of Combined Immunogenicity Results 6 Weeks Following the Administration of a Single Dose of ProQuad® (Varicella Virus Potency ≥3.97 log_{10} PFU) or M-M-R® II and VARIVAX® (Per-Protocol Population)

Group	Antigen	n	Observed Response Rate (95% CI)	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 10. The immunogenicity of the refrigerator-stable formulation and the frozen formulation of ProQuad® were shown to be similar.

Table 10 – 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 11. 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 11 – 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 ≥3.97 Log 10 PFU†

		Dose 1 N=1097			Dose 2 N=1097		
Antigen	**Serostatus Cutoff/ Response Criteria**	**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	≥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)
	≥OD Cutoff (gpELISA units)	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 8 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 12. 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 12 – 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)
		Measles†			
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)	171	295.9	100%	41.5%	3.36

Group Number (Description)	n	GMT (95% CI)	Seropositivity Rate (95% CI)	% ≥4-Fold Rise in Titer (95% CI)	Geometric Mean Fold Rise (95% CI)
(M-M-R® II + VARIVAX®)		(262.5,333.5)	(97.9%, 100%)	(34.0%, 49.3%)	(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 Dose 1 of ProQuad Administered Intramuscularly or Subcutaneously

In an open label clinical trial, 405 children 12 through 18 months of age received two doses of ProQuad, administered 30 days apart (an interval not approved in Canada), either intramuscularly (n=202) or subcutaneously (n=203). Antibody responses to measles, mumps, rubella and varicella viruses were measured by ELISAs using sera obtained 30 days post-dose 1, and 6-weeks post-dose 2. For anti-measles virus, anti-mumps virus, anti-rubella virus and anti-varicella virus, seroresponse rates were defined as the percentage of children seronegative at baseline who achieved antibody titers above the respective seroresponse threshold for each assay 30 days post-dose 1 and 6 weeks post-dose 2. Seroresponse thresholds were defined as 255 mIU/mL, 10 EU/mL, 10 IU/mL and 5 gpELISA units for anti-measles virus, anti-mumps virus, anti-rubella virus and anti-varicella virus antibodies, respectively after each dose. For each vaccine antigen at least 87% of enrolled children were seronegative at baseline. The seroresponse

rates to measles, mumps, rubella and varicella viruses after dose 1 were noninferior in the intramuscular group compared to the subcutaneous group in a post hoc analysis (lower bound of the 95% confidence interval for the difference in seroresponse rates [intramuscular group minus subcutaneous group]>-10 %. The proportions of children achieving antibody titers above the seroresponse thresholds for measles, mumps, rubella and varicella viruses after dose 1 were as follows: 100%, 97.4%, 98.4%, and 98.6%, respectively, in the intramuscular group and 97.3%, 91.3%, 100%, and 98.5%, respectively, in the subcutaneous group.

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 8 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 13. 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 Table14. 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 13 – 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)

	ProQuad® + PCV7 (N=510)		ProQuad® followed by PCV7 (N=259)		Difference (percentage points)[a,b] (95% CI)
Assay Parameter	**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 14 – 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® subcutaneously, and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or ProQuad® subcutaneously and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA® 6 weeks later (N=323) [see 8 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 15. 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 16. 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 17. 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 15 – 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)

*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.

Table 16 – 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:	Difference[a] (percentage points): Group 1 - Group 2

			Non-concomitant VAQTA® separate from ProQuad® + PCV7 (N=323)		(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 17 – 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® subcutaneously, 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 8 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 18 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 18 – 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

		Concomitant Group	Non-Concomitant Group		
		N=949	N=485		
Vaccine Antigen	**Parameter**	**Response**	**Response**	**Risk Difference (95% CI)**	**Criterion for Non-inferiority**
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 = *Haemophilus influenzae* 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. 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.

16 Non-Clinical Toxicology

Carcinogenicity: ProQuad® has not been evaluated for its carcinogenic potential.

Genotoxicity: ProQuad® has not been evaluated for its genotoxicity potential.

Reproductive and Developmental Toxicology: ProQuad® has not been evaluated for its potential to impair fertility. It is also not known whether ProQuad® can cause harm to the fetus when administered to a pregnant woman.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ProQuad®

Measles, Mumps, Rubella and Varicella Virus Vaccine Live

This Patient Medication Information is written for the person who will be taking **ProQuad®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.
This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ProQuad®**, talk to a healthcare professional.

What ProQuad® is used for:

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

How ProQuad® works:

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

Measles 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 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.

Chickenpox (varicella) 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 chickenpox 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 of chickenpox have significantly fallen since the introduction of a varicella vaccine in 1995.

The ingredients in ProQuad® are:

Medicinal ingredient:

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

Non-medicinal ingredients:

ProQuad® contains gelatin, 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.

ProQuad® comes in the following dosage forms:

- ProQuad® is a lyophilized powder for injection
- ProQuad® is available in a pack of 10 single dose vials (lyophilized vaccine and a separate package of vial of diluent)

Do not use ProQuad® if:

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)

To help avoid side effects and ensure proper use, talk to your healthcare professional before your child gets ProQuad®. Talk about any health conditions or problems your child may have, including if your child:

- has any allergies (especially to neomycin).
- has a history of seizures or a brain injury
- has a low blood platelet count
- has received blood or plasma transfusions or administration of human serum globulin within the last 5 months.
- has a family member with a weakened immune system

In rare circumstances, it is possible to catch chickenpox, including severe chickenpox, from a person who has been vaccinated with ProQuad®. This may occur in persons who have not previously been

vaccinated against chickenpox or had chickenpox, as well as persons who fall into one of the following categories:

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

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

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 breastfeeding

- Tell the doctor if the vaccine recipient is breastfeeding or intends to breastfeed. Your doctor will decide if ProQuad® should be given.

Tell your healthcare professional about all the medicines your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ProQuad®:

- 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).
- 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®.
- 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 chickenpox infection has been associated with Reye Syndrome (see How does ProQuad® work?)

How to take ProQuad®:

ProQuad® will be given to your child by a healthcare professional in a healthcare setting.

Usual dose:

ProQuad® is given by intramuscular or 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:

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

If you think you, or a person you are caring for, have taken too much ProQuad®, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using ProQuad®:

These are not all the possible side effects your child may have when taking ProQuad®. If your child experiences any side effects not listed here, tell your healthcare professional.

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 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; shingles (herpes zoster)†; inflammation of the brain and spinal cord (encephalitis†); inflammation of the coverings of the brain and spinal cord (meningitis)†, 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 chickenpox (varicella).

† Can be from naturally occurring chickenpox or the vaccine in healthy individuals or individuals with lowered immunity in those given VARIVAX®.

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 Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Merck Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:
Keep out of reach and sight of children.

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 the Patient Medication Information by visiting the Health Canada Drug Product Database website:(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

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