HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ProQuad safely and effectively. See full prescribing information for ProQuad.

ProQuad®
Measles, Mumps, Rubella and Varicella Virus Vaccine Live
Lyophilized preparation for subcutaneous injection
Initial U.S. Approval: 2005

----------INDICATIONS AND USAGE----------
ProQuad is a vaccine indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age. (1)

---------- DOSAGE AND ADMINISTRATION ----------
A 0.5-mL dose for subcutaneous injection only. (2.1)
- The first dose is usually administered at 12 to 15 months of age. (2.1)
- A second dose, if needed, is usually administered at 4 to 6 years of age. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Suspension for injection (0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using only accompanying sterile diluent. (2.2, 3)

----------CONTRAINDICATIONS----------
- History of anaphylactic reaction to neomycin or hypersensitivity to gelatin or any other component of the vaccine. (4.1)
- Primary or acquired immunodeficiency states. (4.2)
- Family history of congenital or hereditary immunodeficiency. (4.2)
- Immunosuppressive therapy. (4.2, 7.3)
- Active untreated tuberculosis or febrile illness (>101.3°F or >38.5°C). (4.3)
- Pregnancy. (4.4, 8.1, 17)

---------- WARNINGS AND PRECAUTIONS----------
- Administration of ProQuad (dose 1) to children 12 to 23 months old who have not been previously vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections, is 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. (5.1, 6.1, 6.3)
- Use caution when administering ProQuad to children with a history of cerebral injury or seizures or any other condition in which stress due to fever should be avoided. (5.2)
- Use caution when administering ProQuad to children with anaphylaxis or immediate hypersensitivity to eggs (5.3) or contact hypersensitivity to neomycin. (5.4)
- Use caution when administering ProQuad to children with thrombocytopenia. (5.5)
- Avoid close contact with high-risk individuals susceptible to varicella since transmission of varicella vaccine virus may occur between vaccinees and susceptible contacts. (5.8)
- Defer vaccination for at least 3 months following blood or plasma transfusions, or administration of immune globulins (IG). (5.9, 7.1)
- Avoid using salicylates for 6 weeks after vaccination with ProQuad. (6.1, 7.2, 17)
- Avoid pregnancy for 3 months following vaccination with measles, mumps, rubella, and/or varicella vaccines. (8.1, 17)

---------- ADVERSE REACTIONS ----------
- The most frequent vaccine-related adverse events reported in ≥5% of subjects vaccinated with ProQuad were:
  - injection-site reactions (pain/tenderness/soreness, erythema, and swelling)
  - fever
  - irritability. (6.1)
- Systemic vaccine-related adverse events that were reported at a significantly greater rate in recipients of ProQuad than in recipients of the component vaccines administered concomitantly were:
  - fever
  - measles-like rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS or exposure during pregnancy or within three months prior to conception, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------
- Tuberculin testing should be administered anytime before, simultaneously with, or at least 4 to 6 weeks after ProQuad. (7.4)
- ProQuad may be administered concomitantly with *Haemophilus influenzae* type b conjugate vaccine and/or hepatitis B vaccine at separate injection sites. (7.5)
- ProQuad may be administered concomitantly with pneumococcal 7-valent conjugate vaccine and/or hepatitis A vaccine (inactivated) at separate injection sites. (7.5)

---------- USE IN SPECIFIC POPULATIONS ----------
Pregnancy: Do not administer ProQuad to females who are pregnant; the possible effects of the vaccine on fetal development are unknown at this time. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ProQuad® is a vaccine indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

FOR SUBCUTANEOUS ADMINISTRATION ONLY

Each 0.5-mL dose of ProQuad is administered subcutaneously.

The first dose is usually administered at 12 to 15 months of age but may be given anytime through 12 years of age.

If a second dose of measles, mumps, rubella, and varicella vaccine is needed, ProQuad may be used. This dose is usually administered at 4 to 6 years of age. At least 1 month should elapse between a dose of a measles-containing vaccine such as M-M-R® II (measles, mumps, and rubella virus vaccine live) and a dose of ProQuad. At least 3 months should elapse between a dose of varicella-containing vaccine and ProQuad.

2.2 Preparation for Administration

CAUTION: Preservatives, antiseptics, detergents, and other anti-viral substances may inactivate the vaccine. Use only sterile syringes that are free of preservatives, antiseptics, detergents, and other anti-viral substances for reconstitution and injection of ProQuad.

Withdraw the entire volume of the supplied diluent into a syringe. Use only the diluent supplied with the vaccine since it is free of preservatives or other anti-viral substances.

Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Visually inspect the vaccine before and after reconstitution prior to administration. 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.

Withdraw the entire amount of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

TO MINIMIZE LOSS OF POTENCY, THE VACCINE SHOULD BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION. IF NOT USED IMMEDIATELY, THE RECONSTITUTED VACCINE MAY BE STORED AT ROOM TEMPERATURE, PROTECTED FROM LIGHT, FOR UP TO 30 MINUTES. DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

2.3 Method of Administration

Inject the vaccine subcutaneously into the outer aspect of the deltoid region of the upper arm or into the higher anterolateral area of the thigh.

Use With Other Vaccines

Use different injection sites to administer each vaccine if other vaccines are administered concomitantly. *[See Drug Interactions (7.5).]*

3 DOSAGE FORMS AND STRENGTHS

ProQuad is a suspension for injection supplied as a 0.5-mL single dose vial of lyophilized vaccine to be reconstituted using the sterile diluent supplied *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer ProQuad to individuals with a history of anaphylactic reactions to neomycin. If vaccination with ProQuad is medically necessary for such individuals, they are advised to consult an allergist or immunologist and should receive ProQuad only in settings where anaphylactic reactions can be appropriately managed.

Do not administer ProQuad to individuals with a history of hypersensitivity to gelatin or any other component of the vaccine or following previous vaccination with ProQuad, VARIVAX® (varicella virus vaccine live), or any measles-, mumps-, or rubella-containing vaccine *[see Description (11) and Warnings and Precautions (5) for exceptions]*.

4.2 Immunosuppression

Do not administer ProQuad to individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or to individuals on immunosuppressive therapy (including high-dose systemic corticosteroids) *[see Drug Interactions (7.3)]*. Vaccination with a live, attenuated vaccine, such as varicella, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressive drugs. ProQuad may be used by 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.

Do not administer ProQuad to individuals with primary and acquired immunodeficiency states, including 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. In addition, disseminated varicella vaccine virus infection has been reported in children with underlying immunodeficiency disorders who were inadvertently vaccinated with a varicella-containing vaccine {1}.

Do not administer ProQuad to individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

4.3 Concurrent Illness

Do not administer ProQuad to individuals with active untreated tuberculosis or to individuals with an active febrile illness with fever >101.3°F (>38.5°C).

4.4 Pregnancy

Do not administer ProQuad to individuals who are pregnant; the possible effects of the vaccine on fetal development are unknown at this time *[see Use in Specific Populations (8.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Fever and Febrile Seizures

Administration of ProQuad (dose 1) to children 12 to 23 months old who have not been previously vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections, is associated with higher rates of fever and febrile seizures at 5 to 12 days after vaccination when compared to children vaccinated with dose 1 of both M-M-R II and VARIVAX administered separately *[see Adverse Reactions (6.3)]*.

5.2 History of Cerebral Injury or Seizures

Exercise caution when administering ProQuad to persons with a history of cerebral injury, individual or family history of convulsions, or any other condition in which stress due to fever should be avoided. Healthcare providers should be alert to the temperature elevations that may occur following vaccination.

5.3 Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic or other immediate hypersensitivity 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. Carefully evaluate the potential risk-to-benefit ratio before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution; adequate treatment should be readily available should a reaction occur *[see Contraindications (4.1)]* {2}.

Children with egg allergy are at low risk for anaphylactic reactions to measles-containing vaccines (including M-M-R II), and skin testing of children allergic to eggs is not predictive of reactions to M-M-R II vaccine. Persons with allergies to chickens or feathers are not at increased risk of reaction to the vaccine {2}.

5.4 Contact Hypersensitivity to Neomycin

Most often, neomycin allergy manifests as a contact dermatitis, which is not a contraindication to receiving measles-, mumps-, rubella-, or varicella-containing vaccine.

5.5 Thrombocytopenia

Carefully evaluate the potential risk-to-benefit ratio before considering vaccination with ProQuad in children with thrombocytopenia or in those who experienced thrombocytopenia after vaccination with a previous dose of measles, mumps, rubella, and/or varicella vaccine. No clinical data are available regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad. Cases of thrombocytopenia have been reported after primary vaccination with measles vaccine; measles, mumps, and rubella vaccine; after varicella vaccination; and following re-vaccination with measles vaccine or M-M-R II *[see Adverse Reactions (6.2)]*.

5.6 Use for Post-Exposure Prophylaxis

The safety and efficacy of ProQuad for use after exposure to measles, mumps, rubella, or varicella have not been established.

5.7 Use in HIV-Infected Children

The safety and efficacy of ProQuad for use in children known to be infected with human immunodeficiency viruses have not been established.

5.8 Risk of Vaccine Virus Transmission

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

High-risk individuals susceptible to varicella include:

- Immunocompromised individuals;
- Pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection;
- Newborn infants of mothers without documented positive history of varicella or laboratory evidence of prior infection and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

Vaccine recipients should attempt to avoid, to the extent 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.

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 Use in Specific Populations (8.3)]*.

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.

5.9 Immune Globulins and Transfusions

Immune globulins (IG) administered concomitantly with ProQuad contain antibodies that may interfere with vaccine virus replication and decrease the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of IG.

The appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (*e.g.*, 5 months for Varicella Zoster Immune Globulin [VZIG]) {2}. Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination {2}. *[See Drug Interactions (7.1).]*

5.10 Risk of Transmission of Creutzfeldt-Jakob Disease and Other Adventitious Agents

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), no cases of transmission of CJD or viral disease have ever been identified that were associated with the use of albumin. The cells, virus pools, bovine serum, and human albumin used in manufacturing are all

evaluated and tested to provide assurance that the final product is free of potential adventitious agents *[see Description (11)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.

Children 12 Through 23 Months of Age Who Received a Single Dose of ProQuad

ProQuad was administered to 4497 children 12 through 23 months of age involved in 4 randomized clinical trials without concomitant administration with other vaccines. The safety of ProQuad was compared with the safety of M-M-R II and VARIVAX given concomitantly (N=2038) at separate injection sites. The safety profile for ProQuad was similar to the component vaccines. Children in these studies were monitored for up to 42 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for 98% of children in each group. Few subjects (<0.1%) who received ProQuad discontinued the study due to an adverse reaction. The race distribution of the study subjects across these studies following a first dose of ProQuad was as follows: 65.2% White; 13.1% African-American; 11.1% Hispanic; 5.8% Asian/Pacific; 4.5% other; and 0.2% American Indian. The racial distribution of the control group was similar to that of the group who received ProQuad. The gender distribution across the studies following a first dose of ProQuad was 52.5% male and 47.5% female. The gender distribution of the control group was similar to that of the group who received ProQuad. Vaccine-related injection-site and systemic adverse reactions observed among recipients of ProQuad or M-M-R II and VARIVAX at a rate of at least 1% are shown in Table 1. Systemic vaccine-related adverse reactions that were reported at a significantly greater rate in individuals who received a first dose of ProQuad than in individuals who received first doses of M-M-R II and VARIVAX concomitantly at separate injection sites were fever (≥102°F [≥38.9°C] oral equivalent or abnormal) (21.5% versus 14.9%, respectively, risk difference 6.6%, 95% CI: 4.6, 8.5), and measles-like rash (3.0% versus 2.1%, respectively, risk difference 1.0%, 95% CI: 0.1, 1.8). 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 26.8%, respectively, risk difference -4.8%, 95% CI: -7.1, -2.5). The only vaccine-related injection-site adverse reaction that was more frequent among recipients of ProQuad than recipients of M-M-R II and VARIVAX was rash at the injection site (2.4% versus 1.6%, respectively, risk difference 0.9%, 95% CI: 0.1, 1.5).

Table 1: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad Dose 1 or M-M-R II and VARIVAX at 12 to 23 Months of Age (0 to 42 Days Postvaccination)

Adverse Reactions	ProQuad (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, oral equivalent) or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Rubella-like rashes were observed in <1% of subjects following a first dose of ProQuad.

In these clinical trials, two cases of herpes zoster were reported among 2108 healthy subjects 12 through 23 months of age who were vaccinated with their first dose of ProQuad and followed for 1 year. Both cases were unremarkable and no sequelae were reported.

Children 15 to 31 Months of Age Who Received a Second Dose of ProQuad

In 5 clinical trials, 2780 healthy children were vaccinated with ProQuad (dose 1) at 12 to 23 months of age and then administered a second dose approximately 3 to 9 months later. The race distribution of the study subjects across these studies following a second dose of ProQuad was as follows: 64.4% White; 14.1% African-American; 12.0% Hispanic; 5.9% other; 3.5% Asian/Pacific; and 0.1% American Indian. The gender distribution across the studies following a second dose of ProQuad was 51.5% male and 48.5% female. Children in these open-label studies were monitored for at least 28 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for approximately 97% of children overall. Vaccine-related injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 2. In these trials, the overall rates of systemic adverse reactions after ProQuad (dose 2) were comparable to, or lower than, those seen with the first dose. In the subset of children who received both ProQuad dose 1 and dose 2 in these trials (N=2408) with follow-up for fever, fever ≥102.2°F (≥38.9°C) was observed significantly less frequently days 1 to 28 after the second dose (10.8%) than after the first dose (19.1%) (risk difference 8.3%, 95% CI: 6.4, 10.3). Fevers ≥102.2°F (≥38.9°C) days 5 to 12 after vaccinations were also reported significantly less frequently after dose 2 (3.9%) than after dose 1 (13.6%) (risk difference 9.7%, 95% CI: 8.1, 11.3). In the subset of children who received both doses and for whom injection-site reactions were reported (N=2679), injection-site erythema was noted significantly more frequently after ProQuad (dose 2) as compared to ProQuad (dose 1) (12.6% and 10.8%, respectively, risk difference -1.8, 95% CI: -3.3, -0.3); however, pain and tenderness at the injection site was significantly lower after dose 2 (16.1%) as compared with after dose 1 (21.9%) (risk difference, 5.8%, 95% CI: 4.1, 7.6). Two children had febrile seizures after ProQuad (dose 2); both febrile seizures were thought to be related to a concurrent viral illness *[see Adverse Reactions (6.3) and Clinical Studies (14)]*. These studies were not designed or statistically powered to detect a difference in rates of febrile seizure between recipients of ProQuad as compared to M-M-R II and VARIVAX. The risk of febrile seizure has not been evaluated in a clinical study comparing the incidence rate after ProQuad (dose 2) with the incidence rate after concomitant M-M-R II (dose 2) and VARIVAX (dose 2). *[See Adverse Reactions (6.1), Children 4 to 6 Years of Age Who Received ProQuad After Primary Vaccination with M-M-R II and VARIVAX.]*

Table 2: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad Dose 1 at 12 to 23 Months of Age and Dose 2 at 15 to 31 Months of Age (1 to 28 Days Postvaccination)

Adverse Reactions	ProQuad Dose 1 (N=3112) (n=3019) %	ProQuad Dose 2 (N=2780) (n=2695) %
Injection-Site		
Pain/tenderness/soreness*	21.4	15.9
Erythema*	10.7	12.4
Swelling*	8.0	8.5
Injection-site bruising	1.1	0.0
Systemic		
Fever*,†	20.4	8.3
Irritability	6.0	2.4
Measles-like/Rubella-like rash	4.3	0.9

Varicella-like/Vesicular rash	1.5	0.1
Diarrhea	1.3	0.6
Upper respiratory infection	1.3	1.4
Rash (not otherwise specified)	1.2	0.6
Rhinorrhea	1.1	1.0

* Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
† Temperature reported as elevated or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Children 4 to 6 Years of Age Who Received ProQuad After Primary Vaccination with M-M-R II and VARIVAX

In a double-blind clinical trial, 799 healthy 4- to 6-year-old children who 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 (N=205) at separate injection sites, or M-M-R II and VARIVAX (N=195) concomitantly at separate injection sites *[see Clinical Studies (14)]*. Children in these studies were monitored for up to 42 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for >98% of children in each group. The race distribution of the study subjects following a dose of ProQuad was as follows: 78.4% White; 12.3% African-American; 3.8% Hispanic; 3.5% other; and 2.0% Asian/Pacific. The gender distribution following a dose of ProQuad was 52.1% male and 47.9% female. Injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 3. *[See Clinical Studies (14).]*

Table 3: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Previously Vaccinated with M-M-R II and VARIVAX Who Received ProQuad + Placebo, M-M-R II + Placebo, or M-M-R II + VARIVAX at 4 to 6 Years of Age (1 to 43 Days Postvaccination)

Adverse Reactions	**ProQuad + Placebo (N=399) (n=397) %**		**M-M-R II + Placebo (N=205) (n=205) %**		**M-M-R II + VARIVAX (N=195) (n=193) %**	
Systemic						
Fever*,†	2.5		2.0		4.1	
Cough	1.3		0.5		0.5	
Irritability	1.0		0.5		1.0	
Headache	0.8		1.5		1.6	
Rhinorrhea	0.5		1.0		0.5	
Nasopharyngitis	0.3		1.0		1.0	
Vomiting	0.3		1.0		0.5	
Upper respiratory infection	0.0		0.0		1.0	
	ProQuad %	Placebo %	M-M-R II %	Placebo %	M-M-R II %	VARIVAX %
Injection-Site						
Pain*	41.1	34.5	36.6	34.1	35.2	36.8
Erythema*	24.4	13.4	15.6	14.1	14.5	15.5
Swelling*	15.6	8.1	10.2	8.8	7.8	10.9
Bruising	3.5	3.8	2.4	3.4	1.6	2.1
Rash	1.5	1.3	0.0	0.0	0.5	0.0
Pruritus	1.0	0.3	0.0	0.0	0.0	1.0
Nodule	0.0	0.0	0.0	0.0	0.0	1.0

* Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
† Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Safety in Trials That Evaluated Concomitant Use with Other Vaccines

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 an open-label clinical trial, 1434 children were randomized to receive ProQuad given 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 concomitantly (N=949) or non-concomitantly with ProQuad given first and the other vaccines 6 weeks later (N=485). No clinically significant differences in adverse events were reported between treatment groups *[see Clinical Studies (14)]*. The race distribution of the study subjects who received ProQuad was as follows: 70.7% White; 10.9% Asian/Pacific; 10.7% African-American; 4.5% Hispanic; 3.0% other; and 0.2% American Indian. The gender distribution of the study subjects who received ProQuad was 53.6% male and 46.4% female.

ProQuad Administered with Pneumococcal 7-valent Conjugate Vaccine and/or Hepatitis A Vaccine, Inactivated

In an open-label clinical trial, 1027 healthy children 12 to 23 months of age were randomized to receive ProQuad (dose 1) and pneumococcal 7-valent conjugate vaccine (dose 4) concomitantly (N=510) or non-concomitantly at different clinic visits (N=517). The race distribution of the study subjects was as follows: 65.2% White; 15.1% African-American; 10.0% Hispanic; 6.6% other; and 3.0% Asian/Pacific. The gender distribution of the study subjects was 54.5% male and 45.5% female. Injection-site and systemic adverse reactions observed among recipients of ProQuad administered concomitantly or non-concomitantly with pneumococcal 7-valent conjugate vaccine at a rate of at least 1% are shown in Table 4. No clinically significant differences in adverse reactions were reported between the concomitant and non-concomitant treatment groups *[see Clinical Studies (14)]*.

Table 4: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad (dose 1) Concomitantly or Non-Concomitantly with PCV7* (dose 4) at the First Visit (1 to 28 Days Postvaccination)

Adverse Reactions	ProQuad + PCV7 (N=510) (n=498) %	PCV7 (N=258) (n=250) %	ProQuad (N=259) (n=255) %
Injection-Site - ProQuad			
Pain†	24.9	N/A	24.7
Erythema†	12.4	N/A	11.0
Swelling†	10.8	N/A	7.5
Bruising	2.0	N/A	1.6
Injection-Site - PCV7			
Pain†	30.5	29.6	N/A
Erythema†	21.1	24.4	N/A
Swelling†	17.9	20.0	N/A
Bruising	1.6	1.2	N/A
Systemic			
Fever†,‡	15.5	10.0	15.3
Measles-like rash	4.4	0.8	5.1
Irritability	3.8	3.6	3.5
Upper respiratory infection	1.6	0.8	1.2
Varicella-like/vesicular rash	1.6	0.0	1.2
Diarrhea	0.8	1.2	1.2
Vomiting	0.6	0.8	1.2
Rash	0.4	0.0	1.2
Somnolence	0.0	0.0	1.2

* PCV7 = Pneumococcal 7-valent conjugate vaccine, dose 4.
† Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
‡ Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.
N/A = Not applicable.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

In an open-label clinical trial, 699 healthy children 12 to 23 months of age were randomized to receive 2 doses of VAQTA® (hepatitis A vaccine, inactivated) (N=352) or 2 doses of VAQTA concomitantly with 2 doses of ProQuad (N=347) at least 6 months apart. An additional 1101 subjects received 2 doses of VAQTA alone at least 6 months apart (non-randomized), resulting in 1453 subjects receiving 2 doses of VAQTA alone (1101 non-randomized and 352 randomized) and 347 subjects receiving 2 doses of VAQTA concomitantly with ProQuad (all randomized). The race distribution of the study subjects following

a dose of ProQuad was as follows: 47.3% White; 42.7% Hispanic; 5.5% other; 2.9% African-American; and 1.7% Asian/Pacific. The gender distribution of the study subjects following a dose of ProQuad was 49.3% male and 50.7% female. Vaccine-related injection-site adverse reactions (days 1 to 5 postvaccination) and systemic adverse events (days 1 to 14 post VAQTA and days 1 to 28 post ProQuad vaccination) observed among recipients of VAQTA and ProQuad administered concomitantly with VAQTA at a rate of at least 1% are shown in Tables 5 and 6, respectively. In addition, among the randomized cohort, in the 14 days after each vaccination, the rates of fever (including all vaccine- and non-vaccine-related reports) were significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 1 (22.0%) as compared to subjects given dose 1 of VAQTA without ProQuad (10.8%). However, rates of fever were not significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 2 (12.5%) as compared to subjects given dose 2 of VAQTA without ProQuad (9.4%). In post-hoc analyses, these rates were significantly different for dose 1 (relative risk (RR) 2.03 [95% CI: 1.42, 2.94]), but not dose 2 (RR 1.32 [95% CI: 0.82, 2.13]). Rates of injection-site adverse reactions and other systemic adverse events were lower following a second dose than following the first dose of both vaccines given concomitantly.

Table 5: Vaccine-Related Injection-Site Adverse Reactions Reported in ≥1% of Children Who Received VAQTA or ProQuad Concomitantly with VAQTA 1 to 5 Days After Vaccination with VAQTA or VAQTA and ProQuad

	Dose 1		Dose 2	
Adverse Reactions	**VAQTA (N=1453) (n=1412) %**	**ProQuad + VAQTA (N=347) (n=328) %**	**VAQTA (N=1301) (n=1254) %**	**ProQuad + VAQTA (N=292) (n=264) %**
Injection-Site - VAQTA				
Pain/tenderness*	29.2	27.1	30.1	25.0
Erythema*	13.5	12.5	14.3	11.7
Swelling*	7.1	9.1	9.0	8.0
Injection-site bruising	1.9	2.4	1.0	0.8
Injection-Site - ProQuad				
Pain/tenderness*	N/A	30.5	N/A	26.2
Erythema*	N/A	13.4	N/A	12.9
Swelling*	N/A	6.7	N/A	6.5
Injection-site bruising	N/A	1.5	N/A	0.4

* Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
N/A = Not applicable.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Table 6: Vaccine-Related Systemic Adverse Reactions Reported in ≥1% of Children Who Received VAQTA* or ProQuad Concomitantly with VAQTA 1 to 14 Days After VAQTA or Vaccination with ProQuad and VAQTA and 1 to 28 Days After Vaccination with ProQuad and VAQTA

Adverse Reactions	**Dose 1**			**Dose 2**		
	Days 1 to 14		**Days 1 to 28**	**Days 1 to 14**		**Days 1 to 28**
	VAQTA† (N=1453) (n=1412) %	**ProQuad + VAQTA† (N=347) (n=328) %**	**ProQuad + VAQTA (N=347) (n=328) %**	**VAQTA (N=1301) (n=1254) %**	**ProQuad + VAQTA† (N=292) (n=264) %**	**ProQuad + VAQTA† (N=291) (n=263) %**
Fever‡,§	5.7	14.9	15.2	4.1	8.0	8.4
Irritability	5.8	7.0	7.3	3.5	5.3	5.3
Measles-like rash	0.0	3.4	3.4	0.0	1.1	1.1
Rhinorrhea	0.6	2.7	3.0	0.6	1.1	2.7
Diarrhea	1.5	1.8	2.4	1.7	0.4	0.8
Cough	0.6	2.1	2.1	0.2	0.8	1.5
Vomiting	1.1	0.3	0.9	0.6	0.8	1.1

* Systemic adverse events for subjects given VAQTA alone were collected for 14 days postvaccination.
† Safety follow-up for systemic adverse reactions was 14 days for VAQTA and 28 days for ProQuad + VAQTA.

‡ Designates a solicited adverse reaction.
§ Temperature reported as elevated or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

In an open-label clinical trial, 653 children 12 to 23 months of age were randomized to receive a first dose of ProQuad with VAQTA and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or a first dose of ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly and then vaccinated with VAQTA 6 weeks later (N=323). Approximately 6 months later, subjects received either the second doses of ProQuad and VAQTA concomitantly or the second doses of ProQuad and VAQTA separately. The race distribution of the study subjects was as follows: 60.3% White; 21.6% African-American; 9.5% Hispanic; 7.2% other; 1.1% Asian/Pacific; and 0.3% American Indian. The gender distribution of the study subjects was 50.7% male and 49.3% female. Vaccine-related injection-site and systemic adverse reactions observed among recipients of concomitant ProQuad, VAQTA, and pneumococcal 7-valent conjugate vaccine and ProQuad and pneumococcal 7-valent conjugate vaccine at a rate of at least 1% are shown in Tables 7 and 8. In the 28 days after vaccination with the first dose of ProQuad, the rates of fever (including all vaccine- and non-vaccine-related reports) were comparable in subjects who received the 3 vaccines together (38.6%) as compared with subjects given ProQuad and pneumococcal 7-valent conjugate vaccine (42.7%). The rates of fever in the 28 days following the second dose of ProQuad were also comparable in subjects who received ProQuad and VAQTA together (17.4%) as compared with subjects given ProQuad separately from VAQTA (17.0%). In a post-hoc analysis, these differences were not statistically significant after ProQuad (dose 1) (RR 0.90 [95% CI: 0.75, 1.09]) nor after dose 2 (RR 1.02 [95% CI: 0.70, 1.51]). No clinically significant differences in adverse reactions were reported among treatment groups *[see Clinical Studies (14)]*.

Table 7: Vaccine-Related Injection-Site Adverse Reactions
Reported in ≥1% of Children Who Received ProQuad + VAQTA + PCV7* Concomitantly or VAQTA Alone Followed by ProQuad + PCV7 Concomitantly (1 to 5 Days After a Dose of ProQuad)

Adverse Reactions	Dose 1		Dose 2	
	VAQTA + ProQuad + PCV7 (N=330) (n=311) %	VAQTA Alone Followed by ProQuad + PCV7 (N=323) (n=302) %	VAQTA + ProQuad (N=273) (n=265) %	VAQTA Alone Followed by ProQuad (N=240) (n=230) %
Injection-Site - ProQuad				
Pain/tenderness†	21.2	24.2	18.1	17.0
Erythema†	13.5	11.9	10.6	13.0
Swelling†	7.4	10.9	8.3	11.7
Bruising	1.9	1.3	0.8	0.4
Injection-Site - VAQTA				
Pain/tenderness†	20.6	15.3	17.5	20.3
Erythema†	9.6	11.7	9.1	12.7
Swelling†	6.8	9.5	6.1	7.6
Bruising	1.3	1.1	1.1	1.6
Rash	1.0	0.0	0.4	0.4
Injection-Site - PCV7				
Pain/tenderness†	25.4	27.6	N/A	N/A
Erythema†	16.4	16.6	N/A	N/A
Swelling†	13.2	14.3	N/A	N/A
Bruising	0.6	1.7	N/A	N/A

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
† Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination at each vaccine injection site.
N/A = Not applicable.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Table 8: Vaccine-Related Systemic Adverse Reactions
Reported in ≥1% of Children Who Received ProQuad + VAQTA + PCV7* Concomitantly, or VAQTA Alone Followed by ProQuad + PCV7 Concomitantly (1 to 28 Days After a Dose of ProQuad)

Adverse Reactions	Dose 1		Dose 2	
	VAQTA + ProQuad + PCV7 (N=330) (n=311) %	VAQTA Alone Followed by ProQuad + PCV7 (N=323) (n=302) %	VAQTA + ProQuad (N=273) (n=265) %	VAQTA Alone Followed by ProQuad (N=240) (n=230) %
Fever[†,‡]	26.4	27.2	9.1	9.6
Irritability	4.8	6.3	1.9	1.3
Measles-like rash[†]	2.3	4.0	0.0	0.0
Varicella-like rash[†]	1.0	1.7	0.0	0.0
Rash (not otherwise specified)	1.3	1.3	0.0	0.9
Diarrhea	1.3	1.3	0.4	1.3
Upper respiratory infection	1.0	1.3	1.1	0.9
Viral infection	1.0	0.7	0.0	0.0
Rhinorrhea	0.0	0.7	1.1	0.0

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
† Designates a solicited adverse reaction.
‡ Temperature reported as elevated or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Reye syndrome following wild-type varicella infection has occurred in children and adolescents, the majority of whom had received salicylates. In all clinical studies of ProQuad or VARIVAX, the recommendation was made to avoid the use of salicylates for 6 weeks after vaccination. There were no reports of Reye syndrome in recipients of ProQuad or VARIVAX during these studies *[see Drug Interactions (7.2) and Patient Counseling Information (17)]*.

6.2 Post-Marketing Experience

The following adverse events have been identified during post-approval use of either the components of ProQuad or ProQuad. Because the reactions are in some cases described in the literature or reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

Post-Marketing Reports

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

Infections and infestations

Atypical measles, candidiasis, cellulitis, herpes zoster, infection, influenza, measles, orchitis, parotitis, respiratory infection, skin infection, varicella (vaccine strain).

Blood and the lymphatic system disorders

Aplastic anemia, lymphadenitis, regional lymphadenopathy, thrombocytopenia.

Immune system disorders

Anaphylactoid reaction, anaphylaxis and related phenomena such as angioneurotic edema, facial edema, and peripheral edema, anaphylaxis in individuals with or without an allergic history.

Psychiatric disorders

Agitation, apathy, nervousness.

Nervous system disorders

Acute disseminated encephalomyelitis (ADEM), afebrile convulsions or seizures, aseptic meningitis (see below), ataxia, Bell's palsy, cerebrovascular accident, convulsion, dizziness, dream abnormality, encephalitis (see below), encephalopathy (see below), febrile seizure, Guillain-Barré syndrome, headache, hypersomnia, measles inclusion body encephalitis *[see Contraindications (4.2)]*, ocular palsies, paraesthesia, polyneuritis, polyneuropathy, subacute sclerosing panencephalitis (see below), syncope, transverse myelitis, tremor.

Eye disorders

Edema of the eyelid, irritation, necrotizing retinitis (in immunocompromised individuals), optic neuritis, retinitis, retrobulbar neuritis.

Ear and labyrinth disorders

Ear pain, nerve deafness.

Vascular disorders

Extravasation.

Respiratory, thoracic and mediastinal disorders

Bronchial spasm, bronchitis, epistaxis, pneumonitis *[see Contraindications (4.3)]*, pneumonia, pulmonary congestion, rhinitis, sinusitis, sneezing, sore throat, wheezing.

Gastrointestinal disorders

Abdominal pain, flatulence, hematochezia, mouth ulcer.

Skin and subcutaneous tissue disorders

Erythema multiforme, Henoch-Schönlein purpura, herpes simplex, impetigo, panniculitis, pruritus, purpura, skin induration, Stevens-Johnson syndrome, sunburn.

Musculoskeletal, connective tissue and bone disorders

Arthritis and/or arthralgia (usually transient and rarely chronic, see below); musculoskeletal pain; myalgia; pain of the hip, leg, or neck; swelling.

Reproductive system and breast disorders

Epididymitis.

General disorders and administration site conditions

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

Deaths have been reported following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals. Death as a direct consequence of disseminated measles vaccine virus infection has been reported in severely immunocompromised individuals in whom a measles-containing vaccine is contraindicated and who were inadvertently vaccinated. However, there were no deaths or permanent sequelae 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 {3}.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of M-M-R II or measles-, mumps-, and rubella-containing vaccine administered since licensure of these vaccines. The risk of serious neurological disorders following live measles virus vaccine administration remains less than the risk of encephalitis and encephalopathy following infection with wild-type measles (1 per 1000 reported cases) {4,5}.

In severely immunocompromised individuals who have been inadvertently vaccinated with measles-containing vaccine; measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported *[see Contraindications (4.2)]*. In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

Recipients of rubella vaccine may develop chronic joint symptoms. Arthralgia and/or arthritis, and polyneuritis after wild-type rubella virus infection vary in frequency and severity with age and gender, being greatest in adult females and least in pre-pubertal children. Following vaccination in children, reactions in joints are uncommon (0 to 3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are higher than those seen in children (12 to 26%), and the reactions tend to be more marked and of longer duration (*e.g.*, months or years). In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and adult women.

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. Chronic joint symptoms have been reported following administration of rubella-containing vaccine.

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. The association with wild-type measles virus infection is 6 to 22 cases of SSPE per million cases of measles. The results

of a retrospective case-controlled study 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 to Vaccine Adverse Event Reporting System (VAERS) 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.

Cases of thrombocytopenia have been reported after use of measles vaccine; measles, mumps, and rubella vaccine; and after varicella vaccination. 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 testing for antibody to measles, mumps, or rubella should be considered in order to determine if additional doses of vaccine are needed *[see Warnings and Precautions (5.5)]*.

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 {6}. In clinical trials, 8 cases of herpes zoster were reported in 9454 vaccinated individuals 12 months to 12 years of age during 42,556 person-years of follow-up. This resulted in a calculated incidence of at least 18.8 cases per 100,000 person-years. All 8 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.

6.3 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) [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 9. 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 9: 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 VARIVAX. In addition, detailed general safety data were available from more than 25,000 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.

7 DRUG INTERACTIONS

7.1 Immune Globulins and Transfusions

Immune globulins (IG) administered concomitantly with ProQuad contain antibodies that may interfere with vaccine virus replication and decrease the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of IG.

The appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (*e.g.*, 5 months for Varicella Zoster Immune Globulin [VZIG]) {2}. Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination {2}. *[See Warnings and Precautions (5.9).]*

7.2 Salicylates

Reye syndrome has been reported following the use of salicylates during wild-type varicella infection. Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad. *[See Adverse Reactions (6.1) and Patient Counseling Information (17).]*

7.3 Corticosteroids and Immunosuppressive Drugs

ProQuad may be used in individuals who are receiving topical corticosteroids or low-dose corticosteroids for asthma prophylaxis or replacement therapy, *e.g.*, for Addison's disease. ProQuad should not be given to individuals receiving immunosuppressive doses of corticosteroids or other immunosuppressive drugs. Vaccination with a live, attenuated vaccine, such as varicella or measles, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressive drugs *[see Contraindications (4.2)].*

7.4 Drug/Laboratory Test Interactions

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.

7.5 Use with Other Vaccines

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, and at least 3 months should elapse between administration of 2 doses of ProQuad or varicella-containing vaccines.

ProQuad may be administered concomitantly with *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant). Additionally, ProQuad may be administered concomitantly with pneumococcal 7-valent conjugate vaccine, and/or hepatitis A (inactivated) vaccines. *[See Clinical Studies (14).]*

There are no data regarding the administration of ProQuad with inactivated poliovirus vaccine or with other live virus vaccines.

There are insufficient data to support concomitant vaccination with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed. *[See Clinical Studies (14).]*

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category: Contraindication *[see Contraindications (4.4)]*.

Do not administer ProQuad to pregnant females. It is also not known whether ProQuad can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. *[See Contraindications (4.4) and Patient Counseling Information (17).]*

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the healthcare provider 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 {7}; (3) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome {8}; and (4) Wild-type varicella can sometimes cause congenital varicella infection.

Pregnancy Registry

From 1995 to 2013, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintained a Pregnancy Registry to monitor fetal outcomes following inadvertent administration of VARIVAX during pregnancy or within three months prior to conception. In 2006, reports of exposure to two other varicella (Oka/Merck)-containing vaccines, ProQuad and ZOSTAVAX® (Zoster Vaccine Live), were added to the Registry. The Pregnancy Registry has been discontinued. As of March 2011, 811 women with pregnancy outcome information available for analysis were prospectively enrolled following vaccination with VARIVAX, within three months prior to conception or any time during pregnancy. Of these women, 170 were seronegative at the time of exposure and 627 women had an unknown serostatus. The remaining women were seropositive. Nine exposures to either ProQuad or ZOSTAVAX have been reported that met criteria for inclusion into the Registry.

None of the 820 women who received a varicella-containing vaccine delivered infants with abnormalities consistent with congenital varicella syndrome.

All exposures to VARIVAX, ProQuad, or ZOSTAVAX during pregnancy or within three months prior to conception should be reported as suspected adverse reactions by contacting Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

8.3 Nursing Mothers

Do not administer ProQuad to nursing women. It is not known whether ProQuad is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ProQuad is administered to a nursing woman. The secretion of measles and mumps viruses in human milk has not been studied; however, studies have shown that lactating postpartum women vaccinated with live rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. Limited evidence in the literature suggests that virus, viral DNA, or viral antigen could not be detected in the breast milk of women who were vaccinated postpartum with the vaccine strain of varicella virus {9,10}. *[See Warnings and Precautions (5.8).]*

8.4 Pediatric Use

Do not administer ProQuad to infants younger than 12 months of age or to children 13 years and older. Safety and effectiveness of ProQuad in infants younger than 12 months of age and in children 13 years and older have not been studied. ProQuad is not approved for use in persons in these age groups. *[See Adverse Reactions (6) and Clinical Studies (14).]*

8.5 Geriatric Use

ProQuad is not indicated for use in the geriatric population (≥age 65).

11 DESCRIPTION

ProQuad (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) is a combined, attenuated, live virus vaccine containing measles, mumps, rubella, and varicella viruses. ProQuad is a sterile lyophilized preparation of (1) the components of M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live): Measles Virus Vaccine Live, a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; Rubella Virus Vaccine

Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts; and (2) Varicella Virus Vaccine Live (Oka/Merck), the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells. The cells, virus pools, bovine serum, and human albumin used in manufacturing are all tested to provide assurance that the final product is free of potential adventitious agents.

ProQuad, when reconstituted as directed, is a sterile suspension for subcutaneous administration. Each 0.5-mL dose contains not less than 3.00 $\log_{10}$ $TCID_{50}$ 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 of Oka/Merck varicella virus.

Each 0.5-mL dose of the vaccine contains no more than 21 mg of sucrose, 11 mg of hydrolyzed gelatin, 2.4 mg of sodium chloride, 1.8 mg of sorbitol, 0.40 mg of monosodium L-glutamate, 0.34 mg of sodium phosphate dibasic, 0.31 mg of human albumin, 0.17 mg of sodium bicarbonate, 72 mcg of potassium phosphate monobasic, 60 mcg of potassium chloride; 36 mcg of potassium phosphate dibasic; residual components of MRC-5 cells including DNA and protein; <16 mcg of neomycin, bovine calf serum (0.5 mcg), and other buffer and media ingredients. The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ProQuad has been shown to induce measles-, mumps-, rubella-, and varicella-specific immunity, which is thought to be the mechanism by which it protects against these four childhood diseases.

The efficacy of ProQuad was established through the use of immunological correlates for protection against measles, mumps, rubella, and varicella. Results from efficacy studies or field effectiveness studies that were previously conducted for the component vaccines were used to define levels of serum antibodies that correlated with protection against measles, mumps, and rubella. Also, in previous studies with varicella vaccine, antibody responses against varicella virus ≥5 gpELISA units/mL in a glycoprotein enzyme-linked immunosorbent assay (gpELISA) (not commercially available) similarly correlated with long-term protection. In these efficacy studies, the clinical endpoint for measles and mumps was a clinical diagnosis of either disease confirmed by a 4-fold or greater rise in serum antibody titers between either postvaccination or acute and convalescent titers; for rubella, a 4-fold or greater rise in antibody titers with or without clinical symptoms of rubella; and for varicella, varicella-like rash that occurred >42 days postvaccination and for which varicella was not excluded by either viral cultures of the lesion or serological tests. Specific laboratory evidence of varicella either by serology or culture was not required to confirm the diagnosis of varicella. Clinical studies with a single dose of ProQuad have shown that vaccination elicited rates of antibody responses against measles, mumps, and rubella that were similar to those observed after vaccination with a single dose of M-M-R II *[see Clinical Studies (14)]* and seroresponse rates for varicella virus were similar to those observed after vaccination with a single dose of VARIVAX *[see Clinical Studies (14)]*. The duration of protection from measles, mumps, rubella, and varicella infections after vaccination with ProQuad is unknown.

12.4 Persistence of Antibody Responses after Vaccination

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2107 children enrolled in the clinical trials. Antibody was detected in 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) of vaccinees following a single dose of ProQuad.

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 {11}. Varicella antibodies were present for up to ten years postvaccination in most of the individuals tested who received 1 dose of VARIVAX.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ProQuad has not been evaluated for its carcinogenic, mutagenic, or teratogenic potential, or its potential to impair fertility.

14 CLINICAL STUDIES

Formal studies to evaluate the clinical efficacy of ProQuad have not been performed.

Efficacy of the measles, mumps, rubella, and varicella components of ProQuad was previously established in a series of clinical studies with the monovalent vaccines. A high degree of protection from infection was demonstrated in these studies {12-19}.

Immunogenicity in Children 12 Months to 6 Years of Age

Prior to licensure, immunogenicity was studied in 5845 healthy children 12 months to 6 years of age with a negative clinical history of measles, mumps, rubella, and varicella who participated in 5 randomized clinical trials. The immunogenicity of ProQuad was similar to that of its individual component vaccines (M-M-R II and VARIVAX), which are currently used in routine vaccination.

The presence of detectable antibody was assessed by an appropriately sensitive enzyme-linked immunosorbent assay (ELISA) for measles, mumps (wild-type and vaccine-type strains), and rubella, and by gpELISA for varicella. For evaluation of vaccine response rates, a positive result in the measles ELISA corresponded to measles antibody concentrations of ≥255 mIU/mL when compared to the WHO II (66/202) Reference Immunoglobulin for Measles.

Children were positive for mumps antibody if the antibody level was ≥10 ELISA units/mL. A positive result in the rubella ELISA corresponded to concentrations of ≥10 IU rubella antibody/mL when compared to the WHO International Reference Serum for Rubella; children with varicella antibody levels ≥5 gpELISA units/mL were considered to be seropositive since a response rate based on ≥5 gpELISA units/mL has been shown to be highly correlated with long-term protection.

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 10. 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 10: 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 in Children 15 to 31 Months of Age After a Second Dose of ProQuad

In 2 of the 4 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	864	86.6% (84.1%,	11.6 (10.9, 12.3)	864	99.4% (98.7%, 99.8%)	477.5 (437.8, 520.7)

	units		88.8%)				
	≥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 Adverse Reactions (6.1) 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. Post-vaccination 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 Postvaccination 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) (M-M-R II + VARIVAX)	171	295.9 (262.5, 333.5)	100% (97.9%, 100%)	41.5% (34.0%, 49.3%)	3.36 (2.84, 3.97)
		Rubella[‡]			
Group 1 (N=399) (ProQuad + placebo)	367	217.3 (200.1, 236.0)	100% (99.0%, 100%)	32.7% (27.9%, 37.8%)	3.00 (2.72, 3.31)
Group 2 (N=205) (M-M-R II + placebo)	185	174.0 (157.3, 192.6)	100% (98.0%, 100%)	31.9% (25.2%, 39.1%)	2.81 (2.41, 3.27)
Group 3 (N=195) (M-M-R II + VARIVAX)	171	154.1 (138.9, 170.9)	99.4% (96.8%, 100%)	26.9% (20.4%, 34.2%)	2.47 (2.17, 2.81)
		Varicella[§]			
Group 1 (N=399) (ProQuad + placebo)	367	322.2 (278.9, 372.2)	98.9% (97.2%, 99.7%)	80.7 (76.2%, 84.6%)	12.43 (10.63, 14.53)
Group 2 (N=205) (M-M-R II + placebo)	185	N/A	N/A	N/A	N/A
Group 3 (N=195) (M-M-R II + VARIVAX)	171	209.3 (171.2, 255.9)	99.4% (96.8%, 100%)	71.9% (64.6%, 78.5%)	8.50 (6.69, 10.81)

* Measles GMTs are reported in mIU/mL; seropositivity corresponds to ≥120 mIU/mL.
[†] Mumps GMTs are reported in mumps Ab units/mL; seropositivity corresponds to ≥10 Ab units/mL.
[‡] Rubella titers obtained by the legacy format were converted to their corresponding titers in the modified format. Rubella serostatus was determined after the conversion to IU/mL: seropositivity corresponds to ≥10 IU/mL.
[§] Varicella GMTs are reported in gpELISA units/mL; seropositivity rate is reported by % of subjects with postvaccination antibody titers ≥5 gpELISA units/mL. Percentages are calculated as the number of subjects who met the criterion divided by the number of subjects contributing to the per-protocol analysis.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay; ELISA = Enzyme-linked immunosorbent assay; CI = Confidence interval; GMT = Geometric mean titer; N/A = Not applicable; N = Number of subjects vaccinated; n = number of subjects in the per-protocol analysis.

Immunogenicity Following Concomitant Use with Other Vaccines

ProQuad with Pneumococcal 7-valent Conjugate Vaccine and/or VAQTA

In a clinical trial, 1027 healthy children 12 to 15 months of age were randomized to receive ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly (N=510) at separate injection sites or ProQuad and pneumococcal 7-valent conjugate vaccine non-concomitantly (N=517) at separate clinic visits. *[See Adverse Reactions (6.1) 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 Table 14. 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)

Assay Parameter	ProQuad + PCV7 (N=510) n	ProQuad + PCV7 (N=510) Estimated Response[†]	ProQuad followed by PCV7 (N=259) n	ProQuad followed by PCV7 (N=259) Estimated Response[†]	Difference (percentage points)[†,‡] (95% CI)
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.
† Estimated responses and their differences were based on statistical analysis models adjusting for study center.
‡ 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 postvaccination 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)

		Group 1 ProQuad + PCV7 (N=510)		Group 2 PCV7 followed by ProQuad (N=258)		
Serotype	**Parameter**	**n**	**Estimated Response†**	**n**	**Estimated Response†**	**Fold-Difference*,‡ (95% CI)**
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.
† Estimated responses and their fold-difference were based on statistical analysis models adjusting for study center and prevaccination titer.
‡ ProQuad + PCV7 / PCV7 followed by ProQuad.
The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5, (*i.e.*, excluding a decrease of 2-fold or more). This indicates that the fold-difference is statistically significantly less than the pre-specified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.
N = Number of subjects vaccinated in each treatment group; n = Number of subjects contributing to the per-protocol analysis for the given serotype; GMT = geometric mean titer; CI = Confidence interval.

In a clinical trial, 653 healthy children 12 to 15 months of age were randomized to receive VAQTA, ProQuad, and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA 6 weeks later (N=323). *[See Adverse Reactions (6.1) 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)

Parameter	Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)		Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323)		Difference[†] (percentage points): Group 1 – Group 2 (95% CI)
	n	Estimated Response[†]	n	Estimated Response[†]	
% ≥5 gpELISA units/mL[‡]	225[§]	93.2%	232[§]	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.
[†] Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.
[‡] 6 weeks following Dose 1.
[§] 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)

Parameter	Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)		Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323)		Difference[†] (percentage points): Group 1 - Group 2 (95% CI)
	n	Estimated Response[†]	n	Estimated Response[†]	
% ≥10 mIU/mL[‡]	182[§]	100.0%	159[§]	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.
[†] Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.
[‡] 4 weeks following receipt of 2 doses of VAQTA.
[§] 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	

Serotype			ProQuad + PCV7 (N=323)		Fold-Difference† (95% CI)
	n	Estimated Response†	n	Estimated Response†	
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.
† Estimated responses and their fold-difference were based on statistical analysis models adjusting for combined study center and prevaccination titer.
The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5 (*i.e.*, excluding a decrease of 2-fold or more). This indicates that the fold-difference was statistically significantly less than the prespecified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.

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

In a clinical trial, 1913 healthy children 12 to 15 months of age were randomized to receive ProQuad plus diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine concomitantly at separate injection sites (N=949), ProQuad at the initial visit followed by DTaP and *Haemophilus* b conjugate and hepatitis B (recombinant) vaccine given concomitantly 6 weeks later (N=485), or M-M-R II and VARIVAX given concomitantly at separate injection sites (N=479) at the first visit. *[See Adverse Reactions (6.1) 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	89.6%	90.8%	-1.2	LB >-10.0

	units/mL			(-4.1, 2.0)	
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.

15 REFERENCES

1. Levy O, et al. Disseminated varicella infection due to the vaccine strain of varicella-zoster virus, in a patient with a novel deficiency in natural killer T cells. *J Infect Dis.* 188(7):948-53, 2003.
2. Committee on Infectious Diseases, American Academy of Pediatrics. In: Pickering LK, Baker CJ, Overturf GD, et al., eds. Red Book: 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics. 419-29, 2003.
3. Peltola H, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med*. 331(21):1397-1402, 1994.
4. Bennetto L, Scolding N. Inflammatory/post-infectious encephalomyelitis. *J Neurol Neurosurg Psychiatry* 2004;75(Suppl 1):i22-8.
5. Fenichel GM. Neurological complications of immunization. *AnnNeurol* 1982;12(2):119-28.
6. Guess HA, et al. Population-based studies of varicella complications. *Pediatrics*. 78(4 Pt 2):723-727, 1986.
7. Recommendations of the Immunization Practices Advisory Committee (ACIP), Mumps Prevention. *MMWR*. 38(22):388-392, 397-400, 1989.
8. Rubella vaccination during pregnancy--United States, 1971-1986. *MMWR Morb Mortal Wkly Rep*. 36(28):457-61, 1987.
9. Bohlke K, Galil K, Jackson LA, et al. Postpartum varicella vaccination: Is the vaccine virus excreted in breast milk? *Obstetrics and Gynecology*. 102(5):970-977, 2003.
10. Dolbear GL, Moffat J, Falkner C and Wojtowycz M. A Pilot Study: Is attenuated varicella virus present in breast milk after postpartum immunization? *Obstetrics and Gynecology*. 101(4 Suppl.):47S-47S, 2003.
11. Weibel RE, et al. Clinical and laboratory studies of combined live measles, mumps, and rubella vaccines using the RA 27/3 rubella virus. *Proc Soc Exp Biol Med*. 165(2):323-326, 1980.
12. Hilleman MR, Stokes J, Jr., Buynak EB, Weibel R, Halenda R, Goldner H. Studies of live attenuated measles virus vaccine in man: II. appraisal of efficacy. *Am J Public Health.* 52(2):44-56, 1962.
13. Krugman S, Giles JP, Jacobs AM. Studies on an attenuated measles-virus vaccine: VI. clinical, antigenic and prophylactic effects of vaccine in institutionalized children. *N Engl J Med.* 263(4):174-7, 1960.
14. Hilleman MR, Weibel RE, Buynak EB, Stokes J, Jr., Whitman JE, Jr. Live, attenuated mumps-virus vaccine. 4. Protective efficacy as measured in a field evaluation. *N Engl J Med.* 276(5):252-8, 1967.
15. Sugg WC, Finger JA, Levine RH, Pagano JS. Field evaluation of live virus mumps vaccine. *J Pediatr*. 72(4):461-6, 1968.
16. The Benevento and Compobasso Pediatricians Network for the Control of Vaccine-Preventable Diseases, D'Argenio P, Citarella A, Selvaggi MTM. Field evaluation of the clinical effectiveness of vaccines against pertussis, measles, rubella and mumps. *Vaccine*. 16(8):818-22, 1998.
17. Furukawa T, Miyata T, Kondo K, Kuno K, Isomura S, Takekoshi T. Rubella vaccination during an epidemic. *JAMA.* 213(6):987-90, 1970.
18. Vazquez M, et al. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med*. 344(13):955-960, 2001.
19. Kuter B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J*. 23(2):132-137, 2004.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4999 — ProQuad is supplied as follows:

(1) a package of 10 single-dose vials of lyophilized vaccine, NDC 0006-4999-00 (package A)

(2) a separate package of 10 vials of sterile water diluent (package B).

Storage

To maintain potency, ProQuad must be stored frozen between -58°F and +5°F (-50°C to -15°C). Use of dry ice may subject ProQuad to temperatures colder than -58°F (-50°C).

Before reconstitution, store the lyophilized vaccine continuously in a reliably maintained freezer (*e.g.*, chest, frost-free) for up to 18 months.

ProQuad may be stored at refrigerator temperature (36° to 46°F, 2° to 8°C) for up to 72 hours prior to reconstitution. Discard any ProQuad vaccine stored at 36° to 46°F which is not used within 72 hours of removal from 5°F (-15°C) storage.

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

IF NOT USED IMMEDIATELY, THE RECONSTITUTED VACCINE MAY BE STORED AT ROOM TEMPERATURE, PROTECTED FROM LIGHT, FOR UP TO 30 MINUTES.

DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

DO NOT FREEZE RECONSTITUTED VACCINE.

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

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

17 PATIENT COUNSELING INFORMATION

Instructions

Provide the required vaccine information to the patient, parent, or guardian.

Inform the patient, parent, or guardian of the benefits and risks associated with vaccination.

Inform the patient, parent, or guardian that the vaccine recipient should avoid use of salicylates for 6 weeks after vaccination with ProQuad *[see Adverse Reactions (6.1) and Drug Interactions (7.2)]*.

Instruct postpubertal females to avoid pregnancy for 3 months following vaccination *[see Indications and Usage (1) and Use In Specific Populations (8.1)].*

Inform patients, parents, or guardians that vaccination with ProQuad may not offer 100% protection from measles, mumps, rubella, and varicella infection.

Instruct patients, parents, or guardians to report any adverse reactions to their health care provider. The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at http://www.vaers.hhs.gov.

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