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
Refrigerator-stable formulation
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, 17.1)

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)

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, 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)

To report vaccine exposure during pregnancy call 1-800-986-8999.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose and Schedule
2.2 Preparation for Administration
2.3 Method of Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Hypersensitivity
4.2 Immunosuppression
4.3 Concurrent Illness
4.4 Pregnancy
5 WARNINGS AND PRECAUTIONS
5.1 Fever and Febrile Seizures
5.2 History of Cerebral Injuries or Seizures
5.3 Hypersensitivity to Eggs
5.4 Contact Hypersensitivity to Neomycin
5.5 Thrombocytopenia
5.6 Use for Post-Exposure Prophylaxis
5.7 Use in HIV-Infected Children
5.8 Risk of Vaccine Virus Transmission
5.9 Immune Globulins and Transfusions
5.10 Risk of Transmission of Creutzfeldt-Jakob Disease and other Advenitious Agents
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-Marketing Experience
6.3 Post-Marketing Observational Safety Surveillance Study
7 DRUG INTERACTIONS
7.1 Immune Globulins and Transfusions
7.2 Salicylates
7.3 Corticosteroids and Immunosuppressive Drugs
7.4 Drug/Laboratory Test Interactions
ProQuad®
Measles, Mumps, Rubella and Varicella Virus Vaccine Live
Refrigerator-stable formulation

7.5 Use With Other Vaccines

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.4 Persistence of Antibody Responses after Vaccination

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Instructions

*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)].

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.

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

Frozen ProQuad or refrigerator-stable ProQuad was administered to 6038 children 12 through 23 months of age involved in clinical trials without concomitant administration with other vaccines. The safety of frozen ProQuad (N=4497) 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: 67.2% White; 12.0% African-American; 10.6% Hispanic; 5.0% Asian/Pacific; 3.4% other; 1.0% multiracial; 0.2% American Indian; 0.2% European; 0.2% Indian; and 0.1% Polynesian. 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 51.8% male and 48.2% 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 first doses of 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).
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.

Clinical safety of the refrigerator-stable formulation of ProQuad (N=1006) was compared with that of the licensed frozen formulation of ProQuad (N=513) for 42 days postvaccination in children 12 through 23 months of age. The race distribution of the study subjects across these studies following a first dose of ProQuad was as follows: 73.0% White; 9.3% Hispanic; 8.7% African-American; 3.9% multiracial; 2.6% Asian/Pacific; 0.9% Indian; 0.8% European; 0.5% Polynesian, 0.1% American Indian; and 0.1% African. The gender distribution across the studies following a first dose of ProQuad was 49.9% male and 50.1% female.

Injection-site and systemic adverse reactions observed among recipients of ProQuad refrigerator-stable and ProQuad at a rate of at least 1% are shown in Table 2. The safety profiles were comparable for the two different formulations.
ProQuad®
Measles, Mumps, Rubella and Varicella Virus Vaccine Live
Refrigerator-stable formulation

Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ProQuad (refrigerator-stable) (N=1006)</th>
<th>ProQuad (frozen) (N=513)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=963)</td>
<td>(n=500)</td>
</tr>
<tr>
<td>Varicella-like rash†</td>
<td>3.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Eczema</td>
<td>1.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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

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 3. 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: 1.2, 2.4); however, pain and tenderness at the injection site was significantly lower after dose 2 (16.1%) as compared with after dose 1 (21.0%) (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 3
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)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ProQuad Dose 1 (N=3112)</th>
<th>ProQuad Dose 2 (N=2780)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=3019)</td>
<td>(n=2695)</td>
</tr>
<tr>
<td>Injection-Site†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/tenderness/soreness†</td>
<td>21.4</td>
<td>15.9</td>
</tr>
<tr>
<td>Erythema†</td>
<td>10.7</td>
<td>12.4</td>
</tr>
<tr>
<td>Swelling†</td>
<td>8.0</td>
<td>8.5</td>
</tr>
<tr>
<td>Injection-site bruising</td>
<td>1.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>
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 4. [See Clinical Studies (14).]

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ProQuad + Placebo (N=399)</th>
<th>M-M-R II + Placebo (N=205)</th>
<th>M-M-R II + VARIVAX (N=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(% of N=3097)</td>
<td>(% of N=205)</td>
<td>(% of N=193)</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever†‡</td>
<td>2.5</td>
<td>2.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Cough</td>
<td>1.3</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.0</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Headache</td>
<td>0.8</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.3</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Injection-Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain†</td>
<td>41.1</td>
<td>34.5</td>
<td>36.6</td>
</tr>
<tr>
<td>Erythema†</td>
<td>24.4</td>
<td>13.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Swelling‡</td>
<td>15.6</td>
<td>8.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Bruising</td>
<td>3.5</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Rash</td>
<td>1.5</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.0</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Nodule</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

† 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 5. No clinically significant differences in adverse reactions were reported between the concomitant and non-concomitant treatment groups [see Clinical Studies (14)].

Table 5: 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)

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

* 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.
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 6 and 7, 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 (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 6
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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Dose 1</th>
<th>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAQTA</td>
<td>ProQuad + VAQTA†</td>
</tr>
<tr>
<td></td>
<td>(N=1453)</td>
<td>(N=347)</td>
</tr>
<tr>
<td></td>
<td>(n=1412)</td>
<td>(n=328)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Injection-Site VAQTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/tendernessǂ</td>
<td>29.2</td>
<td>27.1</td>
</tr>
<tr>
<td>Erythemaǂ</td>
<td>13.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Swellingǂ</td>
<td>7.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Injection-site bruising</td>
<td>1.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Injection-Site ProQuad</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/tendernessǂ</td>
<td>N/A</td>
<td>30.5</td>
</tr>
<tr>
<td>Erythemaǂ</td>
<td>N/A</td>
<td>13.4</td>
</tr>
<tr>
<td>Swellingǂ</td>
<td>N/A</td>
<td>6.7</td>
</tr>
<tr>
<td>Injection-site bruising</td>
<td>N/A</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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

### Table 7
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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Dose 1</th>
<th>Dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAQTA†</td>
<td>ProQuad + VAQTA†</td>
</tr>
<tr>
<td></td>
<td>(N=1453)</td>
<td>(N=347)</td>
</tr>
<tr>
<td></td>
<td>(n=1412)</td>
<td>(n=328)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Feverǂǂ</td>
<td>5.7</td>
<td>14.9</td>
</tr>
<tr>
<td>Irritability</td>
<td>5.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Measles-like rash</td>
<td>0.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

ǂǂ Designates a solicited adverse reaction. Systemic adverse events were solicited only from Days 1 to 28 postvaccination.

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 8 and 9. 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)].
Reye’s 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’s syndrome in recipients of ProQuad or VARIVAX during these studies [see Drug Interactions (7.2) and Patient Counseling Information (17.1)].

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
- 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, 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, pneumonia [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.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of the combination of measles, mumps, and rubella vaccine contained in M-M-R II. In no case has it been shown conclusively that reactions were actually caused by the vaccine; however, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such
serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (1 per 2000 reported cases).

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 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. 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
ProQuad®
Measles, Mumps, Rubella and Varicella Virus Vaccine Live
Refrigerator-stable formulation

approximate two-fold increase in the risk of febrile seizures in the same 5 to 12 day timeframe after vaccination with ProQuad (dose 1). The incidence of febrile seizures 5 to 12 days after ProQuad (dose 1) (0.70 per 1000 children) was higher than that in children receiving M-M-R II and VARIVAX concomitantly (0.32 per 1000 children) [relative risk (RR) 2.20, 95% confidence interval (CI): 1.04, 4.65]. The incidence of febrile seizures 0 to 30 days after ProQuad (dose 1) (1.41 per 1000 children) was similar to that observed in children receiving M-M-R II and VARIVAX concomitantly [RR 1.10 (95% CI: 0.72, 1.69)]. See Table 10. 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>
<thead>
<tr>
<th>Table 10</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Period</td>
<td>ProQuad cohort (N=31,298)</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>5 to 12 Days</td>
<td>22</td>
</tr>
<tr>
<td>0 to 30 Days</td>
<td>44</td>
</tr>
</tbody>
</table>

In this observational post-marketing study, no case of febrile seizure was observed during the 5 to 12 day postvaccination 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]). Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination. [See Warnings and Precautions (5.9).]

7.2 Salicylates

Reye's 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 (17.1).]

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 C: Animal reproduction studies have not been conducted with ProQuad.

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 post-pubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. [See Contraindications (4.4).]

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; (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, and (4) Wild-type varicella can sometimes cause congenital varicella infection.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to varicella-containing vaccine (Oka/Merck). In the first 9 years of the Pregnancy Registry for varicella vaccine (Oka/Merck), of 129 seronegative women and 423 women of unknown serostatus who received varicella vaccine during pregnancy or within 3 months before pregnancy, none had newborns with abnormalities compatible with congenital varicella syndrome.

Patients and health care providers are encouraged to report any exposure to varicella-containing vaccine (Oka/Merck) during pregnancy by calling 1-800-986-8999.

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. [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 Edmonton 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 nominally contains 20 mg of sucrose, 11 mg of hydrolyzed gelatin, 2.5 mg of urea; 2.3 mg of sodium chloride, 16 mg of sorbitol, 0.38 mg of monosodium L-glutamate, 0.14 mg of sodium bicarbonate, 94 mcg of potassium phosphate, 58 mcg of potassium chloride; residual components of MRC-5 cells including DNA and protein; 5 mcg of neomycin, bovine serum albumin (0.5 mcg), and other buffer and media ingredients. The product contains no preservative.

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. 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.10-17

Immunogenicity in Children 12 Months to 6 Years of Age

Prior to licensure, immunogenicity was studied in 7386 healthy children 12 months to 6 years of age with a negative clinical history of measles, mumps, rubella, and varicella who participated in 6 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 immunogenicity of the refrigerator-stable formulation and the frozen formulation of ProQuad were shown to be similar.

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 11. 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>
<thead>
<tr>
<th>Group</th>
<th>Antigen</th>
<th>n</th>
<th>Observed Response Rate (95% CI)</th>
<th>Observed GMT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProQuad (N=5446)</td>
<td>Varicella</td>
<td>4381</td>
<td>91.2% (90.3%, 92.0%)</td>
<td>15.5 (15.0, 15.9)</td>
</tr>
<tr>
<td></td>
<td>Measles</td>
<td>4733</td>
<td>97.4% (96.9%, 97.9%)</td>
<td>3124.9 (3038.9, 3213.3)</td>
</tr>
<tr>
<td></td>
<td>Mumps (OD cutoff)</td>
<td>973</td>
<td>98.8% (97.9%, 99.4%)</td>
<td>103.3</td>
</tr>
<tr>
<td></td>
<td>Mumps (wild-type ELISA)</td>
<td>3735</td>
<td>95.8% (95.1%, 96.4%)</td>
<td>93.1 (90.2, 96.0)</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>4773</td>
<td>98.8% (98.1%, 98.6%)</td>
<td>91.3 (89.6, 94.1)</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>4773</td>
<td>98.8% (98.1%, 98.6%)</td>
<td>91.3 (89.6, 94.1)</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>4773</td>
<td>98.8% (98.1%, 98.6%)</td>
<td>91.3 (89.6, 94.1)</td>
</tr>
<tr>
<td>M-M-R II + VARIVAX (N=2038)</td>
<td>Varicella</td>
<td>1417</td>
<td>94.1% (92.8%, 95.3%)</td>
<td>16.6 (15.3, 17.9)</td>
</tr>
<tr>
<td></td>
<td>Measles</td>
<td>1516</td>
<td>98.2% (97.4%, 98.8%)</td>
<td>2239.6 (2138.3, 2345.6)</td>
</tr>
<tr>
<td></td>
<td>Mumps (OD cutoff)</td>
<td>501</td>
<td>99.4% (98.3%, 99.9%)</td>
<td>87.5 (79.7, 96.0)</td>
</tr>
<tr>
<td></td>
<td>Mumps (wild-type ELISA)</td>
<td>1017</td>
<td>98.0% (97.0%, 98.8%)</td>
<td>90.8 (86.2, 95.7)</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>1528</td>
<td>98.5% (97.9%, 99.0%)</td>
<td>102.2 (97.8, 106.7)</td>
</tr>
</tbody>
</table>

† 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.

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

<table>
<thead>
<tr>
<th>Assay</th>
<th>Parameter</th>
<th>ProQuad (Refrigerator-Stable) (N=1006)</th>
<th>ProQuad (Frozen) (N=513)</th>
<th>Risk Difference (Percentage Points)†/‡,§ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Estimated Response†</td>
<td>n</td>
<td>Estimated Response†</td>
</tr>
<tr>
<td>Measles</td>
<td>% ≥255 mIU/mL</td>
<td>879</td>
<td>99.1%</td>
<td>452</td>
</tr>
</tbody>
</table>

† 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.
§ 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).
Immunogenicity in Children 15 to 31 Months of Age After a Second Dose of ProQuad

In 2 of the randomized clinical trials described above,\textsuperscript{18,19} 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 13. 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 13 | 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 23.97 Log\textsubscript{10} PFU\textsuperscript{1} |
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 14. Results from this study showed that a first dose of ProQuad after primary vaccination with M-M-R II and VARIVAX elicited a positive antibody response to all four antigens in greater than 98% of subjects. Postvaccination GMTs for recipients of ProQuad were similar to those following a second dose of M-M-R II and VARIVAX administered concomitantly at separate injection sites (the lower bound of the 95% CI around the fold difference in measles, mumps, rubella, and varicella GMTs excluded 0.5). Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of M-M-R II given concomitantly with placebo (the lower bound of the 95% CI around the fold difference for the comparison of measles, mumps, and rubella GMTs excluded 0.5).

Table 14
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)

<table>
<thead>
<tr>
<th>Group Number (Description)</th>
<th>n</th>
<th>GMT (95% CI)</th>
<th>Seropositivity Rate (95% CI)</th>
<th>% ≥4-Fold Rise in Titer (95% CI)</th>
<th>Geometric Mean Fold Rise (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (N=399) (ProQuad + placebo)</td>
<td>367</td>
<td>1985.9</td>
<td>100%</td>
<td>4.9%</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1817.6, 2169.9)</td>
<td>(99.0%, 100%)</td>
<td>(2.9%, 7.6%)</td>
<td>(1.13, 1.30)</td>
</tr>
</tbody>
</table>
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 15. 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 16. 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 15  
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)  

<table>
<thead>
<tr>
<th>Assay Parameter</th>
<th>ProQuad + PCV7 (N=510)</th>
<th>ProQuad followed by PCV7 (N=259)</th>
<th>Difference (percentage points)*b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles % ≥255 mLU/mL</td>
<td>n=406 97.3%</td>
<td>n=204 99.5%</td>
<td>-2.2 (-4.6, 0.2)</td>
</tr>
<tr>
<td>Mumps % ≥10 Ab units/mL</td>
<td>n=403 96.6%</td>
<td>n=208 98.6%</td>
<td>-1.9 (-4.5, 1.0)</td>
</tr>
<tr>
<td>Rubella % ≥10 IU/mL</td>
<td>n=377 98.7%</td>
<td>n=195 97.9%</td>
<td>0.9 (-1.3, 4.1)</td>
</tr>
<tr>
<td>Varicella % ≥5 gpELISA units/mL</td>
<td>n=379 92.5%</td>
<td>n=192 87.9%</td>
<td>4.5 (-0.4, 10.4)</td>
</tr>
</tbody>
</table>

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
  
Seronegative defined as baseline measles antibody titer <255 mLU/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 mLU/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 16  
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)  

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Parameter</th>
<th>Group 1 ProQuad + PCV7 (N=510)</th>
<th>Group 2 PCV7 followed by ProQuad (N=258)</th>
<th>Fold-Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>GMT</td>
<td>n=410 1.5</td>
<td>n=193 1.3</td>
<td>1.2 (1.0, 1.4)</td>
</tr>
<tr>
<td>6B</td>
<td>GMT</td>
<td>n=410 8.3</td>
<td>n=192 8.4</td>
<td>1.1 (0.9, 1.2)</td>
</tr>
<tr>
<td>9V</td>
<td>GMT</td>
<td>n=409 2.9</td>
<td>n=193 2.5</td>
<td>1.2 (1.0, 1.3)</td>
</tr>
<tr>
<td>14</td>
<td>GMT</td>
<td>n=408 6.5</td>
<td>n=193 5.7</td>
<td>1.1 (1.0, 1.3)</td>
</tr>
<tr>
<td>18C</td>
<td>GMT</td>
<td>n=408 2.3</td>
<td>n=193 2.0</td>
<td>1.2 (1.0, 1.3)</td>
</tr>
<tr>
<td>19F</td>
<td>GMT</td>
<td>n=408 3.5</td>
<td>n=192 3.1</td>
<td>1.1 (1.0, 1.3)</td>
</tr>
<tr>
<td>23F</td>
<td>GMT</td>
<td>n=413 4.1</td>
<td>n=197 3.7</td>
<td>1.1 (1.0, 1.3)</td>
</tr>
</tbody>
</table>

* 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 17. 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
ProQuad®
Measles, Mumps, Rubella and Varicella Virus Vaccine Live
Refrigerator-stable formulation

conjugate vaccine as compared to the proportion with a titer $\geq 5$ 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 18. 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 $\geq 10$ 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 19. 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 17
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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)</th>
<th>Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323)</th>
<th>Differencea (percentage points): Group 1 – Group 2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n % ≥5 gpELISA units/mLb</td>
<td>Estimated Responsea 225c 93.2%</td>
<td>Estimated Responsea 232c 98.3%</td>
<td>-5.1 (-9.3, -1.4)</td>
</tr>
</tbody>
</table>

*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.

b 6 weeks following Dose 1.

c Initial Serostatus <1.25 gpELISA units/mL.

The conclusion of similarity (non-inferiority) was based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease of 10 percentage points or more (lower bound >-10.0). This indicated that the risk difference was statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.

Table 18
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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)</th>
<th>Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323)</th>
<th>Differencea (percentage points): Group 1 – Group 2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n % ≥10 mIU/mLb</td>
<td>Estimated Responsea 182c 100.0%</td>
<td>Estimated Responsea 159c 99.3%</td>
<td>0.7 (-1.4, 3.8)</td>
</tr>
</tbody>
</table>

* PCV7 = Pneumococcal 7-valent conjugate vaccine

CI = Confidence interval; N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for hepatitis A.

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

b 4 weeks following receipt of 2 doses of VAQTA.

c Regardless of initial serostatus.

The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the risk difference 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
Table 19
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)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)</th>
<th>Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323)</th>
<th>Fold-Difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>n=246, Estimated Response=1.9</td>
<td>n=247, Estimated Response=1.7</td>
<td>1.1 (0.9, 1.3)</td>
</tr>
<tr>
<td>6B</td>
<td>n=246, Estimated Response=9.9</td>
<td>n=247, Estimated Response=9.4</td>
<td>1.0 (0.8, 1.2)</td>
</tr>
<tr>
<td>9V</td>
<td>n=247, Estimated Response=3.7</td>
<td>n=247, Estimated Response=4.2</td>
<td>0.9 (0.8, 1.0)</td>
</tr>
<tr>
<td>14</td>
<td>n=248, Estimated Response=7.8</td>
<td>n=247, Estimated Response=7.6</td>
<td>1.0 (0.9, 1.2)</td>
</tr>
<tr>
<td>18C</td>
<td>n=247, Estimated Response=2.9</td>
<td>n=247, Estimated Response=2.7</td>
<td>1.1 (0.9, 1.3)</td>
</tr>
<tr>
<td>19F</td>
<td>n=248, Estimated Response=4.0</td>
<td>n=247, Estimated Response=3.6</td>
<td>1.1 (0.9, 1.2)</td>
</tr>
<tr>
<td>23F</td>
<td>n=247, Estimated Response=5.1</td>
<td>n=247, Estimated Response=4.4</td>
<td>1.1 (1.0, 1.3)</td>
</tr>
</tbody>
</table>

* 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 influenzae* 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 influenzae* b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine may be administered concomitantly at separate injection sites (see Table 20 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 20
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

<table>
<thead>
<tr>
<th>Vaccine Antigen Parameter</th>
<th>Concomitant Group N=949</th>
<th>Non-Concomitant Group N=485</th>
<th>Risk Difference (95% CI)</th>
<th>Criterion for Non-inferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles % ≥120 mIU/mL</td>
<td>97.8%</td>
<td>98.7%</td>
<td>-0.9 (-2.3, 0.6)</td>
<td>LB &gt; -5.0</td>
</tr>
<tr>
<td>Mumps % ≥10 ELISA Ab units/mL</td>
<td>95.4%</td>
<td>95.1%</td>
<td>0.3 (-1.7, 2.6)</td>
<td>LB &gt; 5.0</td>
</tr>
<tr>
<td>Rubella % ≥10 IU/mL</td>
<td>98.6%</td>
<td>99.3%</td>
<td>-0.7 (-1.8, 0.5)</td>
<td>LB &gt; 5.0</td>
</tr>
<tr>
<td>Varicella % ≥5 gpELISA units/mL</td>
<td>89.6%</td>
<td>90.8%</td>
<td>-1.2 (-4.1, 2.0)</td>
<td>LB &gt; -10.0</td>
</tr>
<tr>
<td>HiB-PRP % ≥1.0 mcg/mL</td>
<td>94.6%</td>
<td>96.5%</td>
<td>-1.9 (-4.1, 0.8)</td>
<td>LB &gt; -10.0</td>
</tr>
<tr>
<td>HepB % ≥10 mIU/mL</td>
<td>95.9%</td>
<td>98.8%</td>
<td>-2.8 (-4.8, -0.8)</td>
<td>LB &gt; -10.0</td>
</tr>
</tbody>
</table>

HiB-PRP = Haemophilus influenzae type b, polyribosyl phosphate; HepB = hepatitis B; LB = lower bound, limit for non-inferiority comparison.

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4993 — ProQuad is supplied as follows:
(1) a package of 10 single-dose vials of lyophilized vaccine, NDC 0006-4993-41 (package A)
(2) a separate package of 10 vials of sterile water diluent (package B).

Storage
During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 2° to 8°C (36° to 46°F) or colder.

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

DO NOT STORE LYOPHILIZED VACCINE AT ROOM TEMPERATURE.
IF LYOPHILIZED VACCINE IS INADVERTENTLY STORED AT ROOM TEMPERATURE, IT SHOULD BE DISCARDED.
Protect the vaccine from light at all times since such exposure may inactivate the vaccine viruses.

IF NOT USED IMMEDIATELY, THE RECONSITUTED 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.

Diluent vial
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

17.1 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 post-pubertal 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.