**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**
**Suspension for subcutaneous injection**
**Initial U.S. Approval: 2005**

**----------RECENT MAJOR CHANGES----------**
Warnings and Precautions
Risk of Vaccine Virus Transmission (5.6)----------03/2020

**----------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----------**
Administer a 0.5-mL dose of ProQuad subcutaneously. (2.1)
- The first dose is administered at 12 to 15 months of age. (2.1)
- The second dose is 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 accompanying sterile diluent. (2.2, 3)

**----------CONTRAINDICATIONS----------**
- Hypersensitivity to any component of the vaccine. (4.1)
- Immunosuppression. (4.2)
- Moderate or severe febrile illness. (4.3)
- Active untreated tuberculosis. (4.4)
- Pregnancy. (4.5, 8.1)

**----------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. Exercise caution when administering ProQuad to persons with an individual or family history of febrile seizures. (5.1, 6.1, 6.3)
- Use caution when administering ProQuad to children with anaphylaxis or immediate hypersensitivity following egg ingestion. (5.2)
- Use caution when administering ProQuad to children with thrombocytopenia. (5.3)
- Evaluate individuals for immune competence prior to administration of ProQuad if there is a family history of congenital or hereditary immunodeficiency. (5.4)
- Avoid close contact with high-risk individuals susceptible to varicella because of possible transmission of varicella vaccine virus. (5.6)
- Immune Globulins (IG) and other blood products should not be given concurrently with ProQuad. (5.7, 7.1)
- Avoid using salicylates for 6 weeks after vaccination with ProQuad. (5.8, 7.2, 17)

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

**To report SUSPECTED ADVERSE REACTIONS, 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----------**
- Administration of immune globulins and other blood products concurrently with ProQuad vaccine may interfere with the expected immune response. (7.1)
- ProQuad vaccination may result in a temporary depression of purified protein derivative (PPD) tuberculin skin sensitivity. (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. Pregnancy should be avoided for 3 months following vaccination with ProQuad. (4.5, 8.1, 17)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 09/2020**

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## 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

**FOR SUBCUTANEOUS ADMINISTRATION ONLY**

### 2.1 Recommended Dose and Schedule

Each 0.5-mL dose of ProQuad is administered subcutaneously.

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

The second dose is administered at 4 to 6 years of age. At least 1 month should elapse between a dose of a measles-containing vaccine 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

Use a sterile syringe free of preservatives, antiseptics, and detergents for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. To reconstitute, use only the diluent supplied with the vaccine since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

To reconstitute the vaccine, withdraw the entire volume of the supplied diluent from its vial and inject into lyophilized vaccine vial. Agitate to dissolve completely. Discard if the lyophilized vaccine cannot be dissolved.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Visually inspect the vaccine before and after reconstitution prior to administration. Do not use the product if particulates are present or if it appears discolored. 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, inject the entire volume, and discard vial.

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.

## 3 DOSAGE FORMS AND STRENGTHS

ProQuad is a suspension for injection supplied as a single dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]*. A single dose after reconstitution is 0.5 mL.

## 4 CONTRAINDICATIONS

### 4.1 Hypersensitivity

Do not administer ProQuad to individuals with a history of hypersensitivity to any component of the vaccine (including gelatin) {1} or to a previous dose of M-M-R II® (Measles, Mumps, Rubella, Live), ProQuad or VARIVAX® (Varicella Virus Vaccine Live) vaccine, or any other measles, mumps, and rubella or varicella-containing vaccine. Do not administer ProQuad to individuals with a history of anaphylaxis to neomycin *[see Description (11)]*.

### 4.2 Immunosuppression

Do not administer ProQuad vaccine to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy. Measles inclusion body encephalitis {2} (MIBE), pneumonitis {3} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In this population, disseminated mumps and rubella vaccine virus infection have also been reported. Disseminated varicella disease and extensive vaccine-associated rash have been reported in individuals who are immunosuppressed or immunodeficient who were inadvertently vaccinated with a varicella-containing vaccine {4}.

### 4.3 Moderate or Severe Febrile Illness

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

### 4.4 Active Untreated Tuberculosis

Do not administer ProQuad vaccine to individuals with active untreated tuberculosis (TB).

### 4.5 Pregnancy

Do not administer ProQuad to individuals who are pregnant or planning on becoming pregnant in the next 3 months *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)].*

## 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 a first dose of M-M-R II and VARIVAX administered concomitantly *[see Adverse Reactions (6.3)]*. Exercise caution when administering ProQuad to persons with an individual or family history of febrile seizures.

### 5.2 Hypersensitivity to Eggs

Individuals with a history of anaphylactic, anaphylactoid, or other immediate reactions (*e.g.*, hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving ProQuad vaccine. The potential risks and known benefits should be evaluated before considering vaccination in these individuals *[see Contraindications (4.1)]* {5}.

### 5.3 Thrombocytopenia

Transient thrombocytopenia has been reported within 4-6 weeks following vaccination with measles, mumps and rubella vaccine. Carefully evaluate the potential risk and benefit of vaccination in children with thrombocytopenia or in those who experienced thrombocytopenia after vaccination with a previous dose of a measles, mumps, and rubella-containing vaccine *[see Adverse Reactions (6.2)]* {6.8}.

### 5.4 Family History of Immunodeficiency

Vaccination should be deferred in individuals with a family history of congenital or hereditary immunodeficiency until the individual's immune status has been evaluated and the individual has been found to be immunocompetent.

### 5.5 Use in HIV-Infected Individuals

The Advisory Committee on Immunization Practices (ACIP) has recommendations on the use of varicella vaccine in HIV-infected individuals.

### 5.6 Risk of Vaccine Virus Transmission

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

High-risk individuals susceptible to varicella include:

- Immunocompromised individuals;
- 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 (8.2)]*.

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.

### 5.7 Immune Globulins and Transfusions

Immune Globulins (IG) and other blood products should not be given concurrently with ProQuad *[see Drug Interactions (7.1)].* These products may contain antibodies that interfere with vaccine virus replication and decrease the expected immune response.

The ACIP has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

### 5.8 Salicylate Therapy

Avoid the use of salicylates (aspirin) or salicylate-containing products in children and adolescents 12 months through 12 years of age, for six weeks following vaccination with ProQuad due to the association of Reye syndrome with salicylate therapy and wild-type varicella infection *[see Drug Interactions (7.2) and Patient Counseling Information (17)]*.

## 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 practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.

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

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

0.1, 1.8). Both fever and measles-like rash usually occurred within 5 to 12 days following the vaccination, were of short duration, and resolved with no long-term sequelae. Pain/tenderness/soreness at the injection site was reported at a statistically lower rate in individuals who received ProQuad than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites (22.0% versus 26.8%, respectively, risk difference -4.8%, 95% CI: -7.1, -2.5). The only vaccine-related injection-site adverse reaction that was more frequent among recipients of ProQuad than recipients of M-M-R II and VARIVAX was rash at the injection site (2.4% versus 1.6%, respectively, risk difference 0.9%, 95% CI: 0.1, 1.5).

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

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

* Injection-site adverse reactions for M-M-R II and VARIVAX are based on occurrence with either of the vaccines administered.
† Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 0 to 4 postvaccination.
‡ Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

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

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

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

In 5 clinical trials, 2780 healthy children were vaccinated with ProQuad (dose 1) at 12 to 23 months of age and then administered a second dose approximately 3 to 9 months later. The race distribution of the study subjects across these studies following a second dose of ProQuad was as follows: 64.4% White; 14.1% African-American; 12.0% Hispanic; 5.9% other; 3.5% Asian/Pacific; and 0.1% American Indian. The gender distribution across the studies following a second dose of ProQuad was 51.5% male and 48.5% female. Children in these open-label studies were monitored for at least 28 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for approximately 97% of children overall. Vaccine-related injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 2. In these trials, the overall rates of systemic adverse reactions after ProQuad (dose 2) were comparable to, or lower than, those seen with the first dose. In the subset of children who received both ProQuad dose 1 and dose 2 in these trials (N=2408) with follow-up for fever, fever ≥102.2°F (≥38.9°C) was observed significantly less frequently days 1 to 28 after the second dose (10.8%) than after the first dose (19.1%) (risk difference 8.3%, 95% CI: 6.4, 10.3). Fevers ≥102.2°F (≥38.9°C) days 5 to 12 after vaccinations were also reported significantly less frequently after dose 2 (3.9%) than after dose 1 (13.6%) (risk difference 9.7%, 95% CI: 8.1, 11.3). In the subset of children who received both doses and for whom injection-site reactions were reported (N=2679),

injection-site erythema was noted significantly more frequently after ProQuad (dose 2) as compared to ProQuad (dose 1) (12.6% and 10.8%, respectively, risk difference -1.8, 95% CI: -3.3, -0.3); however, pain and tenderness at the injection site was significantly lower after dose 2 (16.1%) as compared with after dose 1 (21.9%) (risk difference, 5.8%, 95% CI: 4.1, 7.6). Two children had febrile seizures after ProQuad (dose 2); both febrile seizures were thought to be related to a concurrent viral illness *[see Adverse Reactions (6.3) and Clinical Studies (14)]*. These studies were not designed or statistically powered to detect a difference in rates of febrile seizure between recipients of ProQuad as compared to M-M-R II and VARIVAX. The risk of febrile seizure has not been evaluated in a clinical study comparing the incidence rate after ProQuad (dose 2) with the incidence rate after concomitant M-M-R II (dose 2) and VARIVAX (dose 2) *[see Adverse Reactions (6.1), Children 4 to 6 Years of Age Who Received ProQuad After Primary Vaccination with M-M-R II and VARIVAX].*

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

| Adverse Reactions | ProQuad Dose 1 (N=3112) (n=3019) % | ProQuad Dose 2 (N=2780) (n=2695) % |
|---|---|---|
| *Injection-Site* | | |
| Pain/tenderness/soreness* | 21.4 | 15.9 |
| Erythema* | 10.7 | 12.4 |
| Swelling* | 8.0 | 8.5 |
| Injection-site bruising | 1.1 | 0.0 |
| *Systemic* | | |
| Fever*,† | 20.4 | 8.3 |
| Irritability | 6.0 | 2.4 |
| Measles-like/Rubella-like rash | 4.3 | 0.9 |
| Varicella-like/Vesicular rash | 1.5 | 0.1 |
| Diarrhea | 1.3 | 0.6 |
| Upper respiratory infection | 1.3 | 1.4 |
| Rash (not otherwise specified) | 1.2 | 0.6 |
| Rhinorrhea | 1.1 | 1.0 |

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

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

In a double-blind clinical trial, 799 healthy 4- to 6-year-old children who received M-M-R II and VARIVAX at least 1 month prior to study entry were randomized to receive ProQuad and placebo (N=399), M-M-R II and placebo concomitantly (N=205) at separate injection sites, or M-M-R II and VARIVAX (N=195) concomitantly at separate injection sites *[see Clinical Studies (14)]*. Children in these studies were monitored for up to 42 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for >98% of children in each group. The race distribution of the study subjects following a dose of ProQuad was as follows: 78.4% White; 12.3% African-American; 3.8% Hispanic; 3.5% other; and 2.0% Asian/Pacific. The gender distribution following a dose of ProQuad was 52.1% male and 47.9% female. Injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 3 *[see Clinical Studies (14)].*

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

| Adverse Reactions | ProQuad + Placebo (N=399) (n=397) % | M-M-R II + Placebo (N=205) (n=205) % | M-M-R II + VARIVAX (N=195) (n=193) % |
|---|---|---|---|

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

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

***Safety in Trials That Evaluated Concomitant Use with Other Vaccines***

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

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

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

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

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

| Adverse Reactions | ProQuad + PCV7 (N=510) (n=498) % | PCV7 (N=258) (n=250) % | ProQuad (N=259) (n=255) % |
|---|---|---|---|
| *Injection-Site - ProQuad* | | | |
| Pain† | 24.9 | N/A | 24.7 |
| Erythema† | 12.4 | N/A | 11.0 |
| Swelling† | 10.8 | N/A | 7.5 |
| Bruising | 2.0 | N/A | 1.6 |

| | | | |
|---|---|---|---|
| *Injection-Site - PCV7* | | | |
| Pain† | 30.5 | 29.6 | N/A |
| Erythema† | 21.1 | 24.4 | N/A |
| Swelling† | 17.9 | 20.0 | N/A |
| Bruising | 1.6 | 1.2 | N/A |
| *Systemic* | | | |
| Fever†,‡ | 15.5 | 10.0 | 15.3 |
| Measles-like rash | 4.4 | 0.8 | 5.1 |
| Irritability | 3.8 | 3.6 | 3.5 |
| Upper respiratory infection | 1.6 | 0.8 | 1.2 |
| Varicella-like/vesicular rash | 1.6 | 0.0 | 1.2 |
| Diarrhea | 0.8 | 1.2 | 1.2 |
| Vomiting | 0.6 | 0.8 | 1.2 |
| Rash | 0.4 | 0.0 | 1.2 |
| Somnolence | 0.0 | 0.0 | 1.2 |

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

In an open-label clinical trial, 699 healthy children 12 to 23 months of age were randomized to receive 2 doses of VAQTA® (hepatitis A vaccine, inactivated) (N=352) or 2 doses of VAQTA concomitantly with 2 doses of ProQuad (N=347) at least 6 months apart. An additional 1101 subjects received 2 doses of VAQTA alone at least 6 months apart (non-randomized), resulting in 1453 subjects receiving 2 doses of VAQTA alone (1101 non-randomized and 352 randomized) and 347 subjects receiving 2 doses of VAQTA concomitantly with ProQuad (all randomized). The race distribution of the study subjects following a dose of ProQuad was as follows: 47.3% White; 42.7% Hispanic; 5.5% other; 2.9% African-American; and 1.7% Asian/Pacific. The gender distribution of the study subjects following a dose of ProQuad was 49.3% male and 50.7% female. Vaccine-related injection-site adverse reactions (days 1 to 5 postvaccination) and systemic adverse events (days 1 to 14 post VAQTA and days 1 to 28 post ProQuad vaccination) observed among recipients of VAQTA and ProQuad administered concomitantly with VAQTA at a rate of at least 1% are shown in Tables 5 and 6, respectively. In addition, among the randomized cohort, in the 14 days after each vaccination, the rates of fever (including all vaccine- and non-vaccine-related reports) were significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 1 (22.0%) as compared to subjects given dose 1 of VAQTA without ProQuad (10.8%). However, rates of fever were not significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 2 (12.5%) as compared to subjects given dose 2 of VAQTA without ProQuad (9.4%). In post-hoc analyses, these rates were significantly different for dose 1 (relative risk (RR) 2.03 [95% CI: 1.42, 2.94]), but not dose 2 (RR 1.32 [95% CI: 0.82, 2.13]). Rates of injection-site adverse reactions and other systemic adverse events were lower following a second dose than following the first dose of both vaccines given concomitantly.

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

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

| | | | | |
|---|---|---|---|---|
| Swelling* | N/A | 6.7 | N/A | 6.5 |
| Injection-site bruising | N/A | 1.5 | N/A | 0.4 |

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

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

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

* Systemic adverse events for subjects given VAQTA alone were collected for 14 days postvaccination.
† Safety follow-up for systemic adverse reactions was 14 days for VAQTA and 28 days for ProQuad + VAQTA.
‡ Designates a solicited adverse reaction.
§ Temperature reported as elevated or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

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

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

| Adverse Reactions | Dose 1 | | Dose 2 | |
|---|---|---|---|---|
| | VAQTA + ProQuad + | VAQTA Alone Followed by | VAQTA + ProQuad (N=273) | VAQTA Alone Followed by |

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

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

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

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

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

## 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 events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

*Infections and infestations*

Subacute sclerosing panencephalitis, encephalitis, aseptic meningitis, meningitis, measles, atypical measles, pneumonia, respiratory infection, infection, varicella (vaccine strain), influenza, herpes zoster, orchitis, epididymitis, cellulitis, skin infection, retinitis, bronchitis, parotitis, sinusitis, impetigo, herpes simplex, candidiasis, rhinitis.

The vaccine virus (Oka/Merck strain) contained in ProQuad may establish latency of varicella zoster virus in immunocompetent individuals, with the potential for later development of herpes zoster.

Cases of encephalitis or meningitis caused by vaccine strain varicella virus have been reported in immunocompetent individuals previously vaccinated with VARIVAX (same varicella vaccine strain as in ProQuad) months to years after vaccination. Reported cases were commonly associated with preceding or concurrent herpes zoster rash.

*Blood and the lymphatic system disorders*

Aplastic anemia, thrombocytopenia, regional lymphadenopathy, lymphadenitis.

*Immune system disorders*

Anaphylaxis and related phenomena such as angioneurotic edema, facial edema, and peripheral edema, anaphylactoid reaction.

*Psychiatric disorders*

Agitation, apathy, nervousness.

*Nervous system disorders*

Measles inclusion body encephalitis, acute disseminated encephalomyelitis, transverse myelitis, cerebrovascular accident, encephalopathy, Guillain-Barré syndrome, optic neuritis, Bell's palsy, polyneuropathy, ataxia, hypersomnia, afebrile convulsions or seizures, febrile seizure, headache, syncope, dizziness, tremor, paraesthesia.

*Eye disorders*

Necrotizing retinitis (in immunocompromised individuals), retrobulbar neuritis, ocular palsies, edema of the eyelid, irritation eye.

*Ear and labyrinth disorders*

Nerve deafness, ear pain.

*Vascular disorders*

Extravasation blood.

*Respiratory, thoracic and mediastinal disorders*

Pneumonitis, pulmonary congestion, wheezing, bronchial spasm, epistaxis, sore throat.

*Gastrointestinal disorders*

Hematochezia, abdominal pain, mouth ulcer.

*Skin and subcutaneous tissue disorders*

Stevens-Johnson syndrome, Henoch-Schönlein purpura, erythema multiforme, acute hemorrhagic edema of infancy, purpura, skin induration, panniculitis, pruritus.

*Musculoskeletal, connective tissue and bone disorders*

Arthritis, arthralgia, pain of the hip, leg, or neck; myalgia; musculoskeletal pain.

*General disorders and administration site conditions*

Injection-site complaints including wheal and flare, warm to touch, stiffness, warm sensation, inflammation, injection-site hemorrhage, injection-site injury.

**6.3 Post-Marketing Observational Safety Surveillance Study**

Safety was evaluated in an observational study that included 69,237 children vaccinated with ProQuad 12 months to 12 years old. A historical comparison group included 69,237 age-, gender-, and date-of-vaccination (day and month)-matched subjects who were given M-M-R II and VARIVAX concomitantly. The primary objective was to assess the incidence of febrile seizures occurring within various time intervals after vaccination in 12- to 60-month-old children who had neither been vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections (N=31,298 vaccinated with ProQuad, including 31,043 who were 12 to 23 months old). The incidence of febrile seizures was also assessed in a historical control group of children who had received their first vaccination with M-M-R II and VARIVAX concomitantly (N=31,298, including 31,019 who were 12 to 23 months old). The secondary objective was to assess the general safety of ProQuad in the 30-day period after vaccination in children 12 months to 12 years old.

In pre-licensure clinical studies, an increase in fever was observed 5 to 12 days after vaccination with ProQuad (dose 1) compared to M-M-R II and VARIVAX (dose 1) given concomitantly. In the post-marketing observational surveillance study, results from the primary safety analysis revealed an approximate two-fold increase in the risk of febrile seizures in the same 5 to 12 day timeframe after vaccination with ProQuad (dose 1). The incidence of febrile seizures 5 to 12 days after ProQuad (dose 1) (0.70 per 1000 children) was higher than that in children receiving M-M-R II and VARIVAX concomitantly

(0.32 per 1000 children) [RR 2.20, 95% confidence interval (CI): 1.04, 4.65]. The incidence of febrile seizures 0 to 30 days after ProQuad (dose 1) (1.41 per 1000 children) was similar to that observed in children receiving M-M-R II and VARIVAX concomitantly [RR 1.10 (95% CI: 0.72, 1.69)]. See Table 9. General safety analyses revealed that the risks of fever (RR=1.89; 95% CI: 1.67, 2.15) and skin eruption (RR=1.68; 95% CI: 1.07, 2.64) were significantly higher after ProQuad (dose 1) compared with those who received concomitant first doses of M-M-R II and VARIVAX, respectively. All medical events that resulted in hospitalization or emergency room visits were compared between the group given ProQuad and the historical comparison group, and no other safety concerns were identified in this study.

**Table 9: Confirmed Febrile Seizures Days 5 to 12 and 0 to 30 After Vaccination with ProQuad (dose 1) Compared to Concomitant Vaccination with M-M-R II and VARIVAX (dose 1) in Children 12 to 60 Months of Age**

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

In this observational post-marketing study, no case of febrile seizure was observed during the 5 to 12 day 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

Administration of immune globulins and other blood products concurrently with ProQuad vaccine may interfere with the expected immune response *[see Warnings and Precautions (5.7)]* {9-11}. The ACIP has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

### 7.2 Salicylates

Reye syndrome has been reported following the use of salicylates during wild-type varicella infection. Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad *[see Warnings and Precautions (5.8) and Patient Counseling Information (17)].*

### 7.3 Corticosteroids and Immunosuppressive Drugs

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

ProQuad vaccine contains live attenuated measles, mumps, rubella and varicella viruses. The vaccine is contraindicated for use in pregnant women because infection during pregnancy with the wild-type viruses is associated with maternal and fetal adverse outcomes.

For women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of administration of ProQuad, 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 infection with wild-type measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy; (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 {12}; (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 {13}; and (4) Wild-type varicella, if acquired during pregnancy, can sometimes cause congenital varicella syndrome.

Available data on inadvertent administration of ProQuad to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

There are no relevant animal data.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively {14,15}.

Data

*Human Data*

In a 10-year CDC 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 {13}.

### 8.2 Lactation

Risk Summary

It is not known whether varicella, measles, or mumps vaccine virus is excreted in human milk. Studies have shown that lactating postpartum women vaccinated with live rubella vaccine may secrete the virus in breast milk and transmit it to breastfed infants *[see Warnings and Precautions (5.6)]* {16,17}.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ProQuad, and any potential adverse effects on the breastfed child from ProQuad or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

### 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 established *[see Clinical Studies (14)].*

### 8.5 Geriatric Use

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

## 11 DESCRIPTION

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

virus propagated in MRC-5 cells. The cells, virus pools, bovine serum, and recombinant 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.

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

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

### 12.6 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 neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in 95-100%, 74-91%, and 90-100% of individuals respectively, 11 to 13 years after primary vaccination series {18-24}. 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 {25-32}.

*Immunogenicity in Children 12 Months to 6 Years of Age*

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

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

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

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

In 4 randomized clinical trials, 5446 healthy children 12 to 23 months of age were administered ProQuad, and 2038 children were vaccinated with M-M-R II and VARIVAX given concomitantly at separate injection sites. Subjects enrolled in each of these trials had a negative clinical history, no known recent exposure, and no vaccination history for varicella, measles, mumps, and rubella. Children were excluded from study participation if they had an immune impairment or had a history of allergy to components of the vaccine(s). Except for in 1 trial *[see ProQuad Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine below]*, no concomitant vaccines were permitted during study participation. The race distribution of the study subjects across these studies following a first dose of ProQuad was as follows: 66.3% White; 12.7% African-American; 9.9% Hispanic; 6.7% Asian/Pacific; 4.2% other; and 0.2% American Indian. The gender distribution of the study subjects across these studies following a first dose of ProQuad was 52.6% male and 47.4% female. A summary of combined immunogenicity results 6 weeks following administration of a single dose of ProQuad or M-M-R II and VARIVAX is shown in Table 10. These results were similar to the immune response rates induced by concomitant administration of single doses of M-M-R II and VARIVAX at separate injection sites (lower bound of the 95% CI for the risk difference in measles, mumps, and rubella seroconversion rates were >-5.0 percentage points and the lower bound of the 95% CI for the risk difference in varicella seroprotection rates was either >-15 percentage points [one study] or >-10.0 percentage points [three studies]).

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

| Group | Antigen | n | Observed Response Rate (95% CI) | Observed GMT (95% CI) |
|---|---|---|---|---|
| ProQuad (N=5446*) | Varicella | 4381 | 91.2% (90.3%, 92.0%) | 15.5 (15.0, 15.9) |
| | Measles | 4733 | 97.4% (96.9%, 97.9%) | 3124.9 (3038.9, 3213.3) |
| | Mumps (OD cutoff)† | 973 | 98.8% (97.9%, 99.4%) | 105.3 (98.0, 113.1) |
| | Mumps (wild-type ELISA)† | 3735 | 95.8% (95.1%, 96.4%) | 93.1 (90.2, 96.0) |
| | Rubella | 4773 | 98.5% (98.1%, 98.8%) | 91.8 (89.6, 94.1) |
| M-M-R II + VARIVAX (N=2038*) | Varicella | 1417 | 94.1% (92.8%, 95.3%) | 16.6 (15.9, 17.4) |
| | Measles | 1516 | 98.2% (97.4%, 98.8%) | 2239.6 (2138.3, 2345.6) |
| | Mumps | 501 | 99.4% | 87.5 |

| | | | | |
|---|---|---|---|---|
| | (OD cutoff)† | | (98.3%, 99.9%) | (79.7, 96.0) |
| | Mumps (wild-type ELISA)† | 1017 | 98.0% (97.0%, 98.8%) | 90.8 (86.2, 95.7) |
| | Rubella | 1528 | 98.5% (97.7%, 99.0%) | 102.2 (97.8, 106.7) |

* Includes ProQuad + Placebo followed by ProQuad (Visit 1) (Protocol 009), ProQuad Middle and High Doses (Visit 1) (Protocol 011), ProQuad (Lot 1, Lot 2, Lot 3) (Protocol 012), both the Concomitant and Non-concomitant groups (Protocol 013).

† The mumps antibody response was assessed by a vaccine-strain ELISA in Protocols 009 and 011 and by a wild-type ELISA in Protocols 012 and 013. In the former assay, the serostatus was based on the OD cutoff of the assay. In the latter assay, 10 mumps ELISA units was used as the serostatus cutoff.

n = Number of per-protocol subjects with evaluable serology.
CI = Confidence interval.
GMT = Geometric mean titer.
ELISA = Enzyme-linked immunosorbent assay.
PFU = Plaque-forming units.
OD = Optical density.

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

In 2 of the 4 randomized clinical trials described above, a subgroup (N=1035) of the 5446 children administered a single dose of ProQuad were administered a second dose of ProQuad approximately 3 to 9 months after the first dose. Children were excluded from receiving a second dose of ProQuad if they were recently exposed to or developed varicella, measles, mumps, and/or rubella prior to receipt of the second dose. No concomitant vaccines were administered to these children. The race distribution across these studies following a second dose of ProQuad was as follows: 67.3% White; 14.3% African-American; 8.3% Hispanic; 5.4% Asian/Pacific; 4.4% other; 0.2% American Indian; and 0.10% mixed. The gender distribution of the study subjects across these studies following a second dose of ProQuad was 50.4% male and 49.6% female. A summary of immune responses following a second dose of ProQuad is presented in Table 11. Results from this study showed that 2 doses of ProQuad administered at least 3 months apart elicited a positive antibody response to all four antigens in greater than 98% of subjects. The geometric mean titers (GMTs) following the second dose of ProQuad increased approximately 2-fold each for measles, mumps, and rubella, and approximately 41-fold for varicella.

**Table 11: Summary of Immune Response to a First and Second Dose of ProQuad in Subjects <3 Years of Age Who Received ProQuad with a Varicella Virus Dose ≥3.97 $Log_{10}$ PFU***

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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | units) | | 89.6%) | | | | |

* Includes the following treatment groups: ProQuad + Placebo followed by ProQuad (Visit 1) (Protocol 009) and ProQuad (Middle and High Dose) (Protocol 011).
† Samples from Protocols 009 and 011 were assayed in the legacy format Measles ELISA, which reported antibody titers in Measles ELISA units. To convert titers from ELISA units to mIU/mL, titers for these 2 protocols were divided by 0.1025. The lowest measurable titer postvaccination is 207.5 mIU/mL. The response rate for measles in the legacy format is the percent of subjects with a negative baseline measles antibody titer, as defined by the optical density (OD) cutoff, with a postvaccination measles antibody titer ≥207.5 mIU/mL.
Samples from Protocols 009 and 011 were assayed in the legacy format Rubella ELISA, which reported antibody titers in Rubella ELISA units. To convert titers from ELISA units to IU/mL, titers for these 2 protocols were divided by 1.28.
ProQuad (Middle Dose) = ProQuad containing a varicella virus dose of 3.97 $\log_{10}$ PFU.
ProQuad (High Dose) = ProQuad containing a varicella virus dose of 4.25 $\log_{10}$ PFU.
ELISA = Enzyme-linked immunosorbent assay.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
N = Number vaccinated at baseline.
n = Number of subjects who were per-protocol Postdose 1 and Postdose 2 and satisfied the given prevaccination serostatus cutoff.
CI = Confidence interval.
GMT = Geometric mean titer.
PFU = Plaque-forming units.

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

In a clinical trial, 799 healthy 4- to 6-year-old children who had received M-M-R II and VARIVAX at least 1 month prior to study entry were randomized to receive ProQuad and placebo (N=399), M-M-R II and placebo concomitantly at separate injection sites (N=205), or M-M-R II and VARIVAX concomitantly at separate injection sites (N=195). Children were eligible if they were previously administered primary doses of M-M-R II and VARIVAX, either concomitantly or non-concomitantly, at 12 months of age or older. Children were excluded if they were recently exposed to measles, mumps, rubella, and/or varicella, had an immune impairment, or had a history of allergy to components of the vaccine(s). No concomitant vaccines were permitted during study participation *[see Adverse Reactions (6.1) for ethnicity and gender information].*

A summary of antibody responses to measles, mumps, rubella, and varicella at 6 weeks postvaccination in subjects who had previously received M-M-R II and VARIVAX is shown in Table 12. Results from this study showed that a first dose of ProQuad after primary vaccination with M-M-R II and VARIVAX elicited a positive antibody response to all four antigens in greater than 98% of subjects. Postvaccination GMTs for recipients of ProQuad were similar to those following a second dose of M-M-R II and VARIVAX administered concomitantly at separate injection sites (the lower bound of the 95% CI around the fold difference in measles, mumps, rubella, and varicella GMTs excluded 0.5). Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of M-M-R II given concomitantly with placebo (the lower bound of the 95% CI around the fold difference for the comparison of measles, mumps, and rubella GMTs excluded 0.5).

**Table 12: Summary of Antibody Responses to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination in Subjects 4 to 6 Years of Age Who Had Previously Received M-M-R II and VARIVAX (Per-Protocol Population)**

| Group Number (Description) | n | GMT (95% CI) | Seropositivity Rate (95% CI) | % ≥4-Fold Rise in Titer (95% CI) | Geometric Mean Fold Rise (95% CI) |
|---|---|---|---|---|---|
| | | **Measles*** | | | |
| Group 1 (N=399) (ProQuad + placebo) | 367 | 1985.9 (1817.6, 2169.9) | 100% (99.0%, 100%) | 4.9% (2.9%, 7.6%) | 1.21 (1.13, 1.30) |
| Group 2 (N=205) (M-M-R II + placebo) | 185 | 2046.9 (1815.2, 2308.2) | 100% (98.0%, 100%) | 4.3% (1.9%, 8.3%) | 1.28 (1.17, 1.40) |
| Group 3 (N=195) (M-M-R II + VARIVAX) | 171 | 2084.3 (1852.3, 2345.5) | 99.4% (96.8%, 100%) | 4.7% (2.0%, 9.0%) | 1.31 (1.17, 1.46) |
| | | **Mumps†** | | | |
| Group 1 (N=399) (ProQuad + placebo) | 367 | 206.0 (188.2, 225.4) | 99.5% (98.0%, 99.9%) | 27.2% (22.8%, 32.1%) | 2.43 (2.19, 2.69) |
| Group 2 (N=205) | 185 | 308.5 | 100% | 41.1% | 3.69 |

| | | | | | |
|---|---|---|---|---|---|
| (M-M-R II + placebo) | | (269.6, 352.9) | (98.0%, 100%) | (33.9%, 48.5%) | (3.14, 4.32) |
| Group 3 (N=195) (M-M-R II + VARIVAX) | 171 | 295.9 (262.5, 333.5) | 100% (97.9%, 100%) | 41.5% (34.0%, 49.3%) | 3.36 (2.84, 3.97) |
| | | **Rubella‡** | | | |
| Group 1 (N=399) (ProQuad + placebo) | 367 | 217.3 (200.1, 236.0) | 100% (99.0%, 100%) | 32.7% (27.9%, 37.8%) | 3.00 (2.72, 3.31) |
| Group 2 (N=205) (M-M-R II + placebo) | 185 | 174.0 (157.3, 192.6) | 100% (98.0%, 100%) | 31.9% (25.2%, 39.1%) | 2.81 (2.41, 3.27) |
| Group 3 (N=195) (M-M-R II + VARIVAX) | 171 | 154.1 (138.9, 170.9) | 99.4% (96.8%, 100%) | 26.9% (20.4%, 34.2%) | 2.47 (2.17, 2.81) |
| | | **Varicella§** | | | |
| Group 1 (N=399) (ProQuad + placebo) | 367 | 322.2 (278.9, 372.2) | 98.9% (97.2%, 99.7%) | 80.7% (76.2%, 84.6%) | 12.43 (10.63, 14.53) |
| Group 2 (N=205) (M-M-R II + placebo) | 185 | N/A | N/A | N/A | N/A |
| Group 3 (N=195) (M-M-R II + VARIVAX) | 171 | 209.3 (171.2, 255.9) | 99.4% (96.8%, 100%) | 71.9% (64.6%, 78.5%) | 8.50 (6.69, 10.81) |

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

*Immunogenicity Following Concomitant Use with Other Vaccines*

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

In a clinical trial, 1027 healthy children 12 to 15 months of age were randomized to receive ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly (N=510) at separate injection sites or ProQuad and pneumococcal 7-valent conjugate vaccine non-concomitantly (N=517) at separate clinic visits *[see Adverse Reactions (6.1) for ethnicity and gender information].* The statistical analysis of non-inferiority in antibody response rates to measles, mumps, rubella, and varicella at 6 weeks postvaccination for subjects are shown in Table 13. In the per-protocol population, seroconversion rates were not inferior in children given ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly when compared to seroconversion rates seen in children given these vaccines non-concomitantly for measles, mumps, and rubella. In children with baseline varicella antibody titers <1.25 gpELISA units/mL, the varicella seroprotection rates were not inferior when rates after concomitant and non-concomitant vaccination were compared 6 weeks postvaccination. Statistical analysis of non-inferiority in GMTs to *S. pneumoniae* serotypes at 6 weeks postvaccination are shown in Table 14. Geometric mean antibody titers (GMTs) for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were not inferior when antibody titers in the concomitant and non-concomitant groups were compared 6 weeks postvaccination.

**Table 13: Statistical Analysis of Non-Inferiority in Antibody Response Rates to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella, or With Varicella Antibody Titer <1.25 gpELISA units at Baseline in the ProQuad + PCV7* Treatment Group and the ProQuad Followed by PCV7 Control Group (Per-Protocol Analysis)**

| Assay Parameter | ProQuad + PCV7 (N=510) | | ProQuad followed by PCV7 (N=259) | | Difference (percentage points)†,‡ (95% CI) |
|---|---|---|---|---|---|
| | n | Estimated Response† | n | Estimated Response† | |
| Measles % ≥255 mIU/mL | 406 | 97.3% | 204 | 99.5% | -2.2 (-4.6, 0.2) |
| Mumps % ≥10 Ab units/mL | 403 | 96.6% | 208 | 98.6% | -1.9 (-4.5, 1.0) |
| Rubella % ≥10 IU/mL | 377 | 98.7% | 195 | 97.9% | 0.9 (-1.3, 4.1) |
| Varicella | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| % ≥5 gpELISA units/mL | 379 | 92.5% | 192 | 87.9% | 4.5 (-0.4, 10.4) |

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
Seronegative defined as baseline measles antibody titer <255 mIU/mL for measles, baseline mumps antibody titer <10 ELISA Ab units/mL for mumps, and baseline rubella antibody titer <10 IU/mL for rubella.
† Estimated responses and their differences were based on statistical analysis models adjusting for study center.
‡ ProQuad + PCV7 - ProQuad followed by PCV7.
The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -10 percentage points (*i.e.*, excluding a decrease equal to or more than the prespecified criterion of 10.0 percentage points). This indicates that the difference is statistically significantly less than the prespecified clinically relevant decrease of 10.0 percentage points at the 1-sided alpha = 0.025 level.
N = Number of subjects vaccinated in each treatment group.
n = Number of subjects with measles antibody titer <255 mIU/mL, mumps antibody titer <10 ELISA Ab units/mL, rubella antibody titer <10 IU/mL, or varicella antibody titer <1.25 gpELISA units/mL at baseline and with postvaccination serology contributing to the per-protocol analysis.
Ab = antibody; ELISA = Enzyme-linked immunosorbent assay; gpELISA = Glycoprotein enzyme-linked immunosorbent assay; CI = Confidence interval.

**Table 14: Statistical Analysis of Non-Inferiority in GMTs to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination in the ProQuad + PCV7* Treatment Group and the PCV7 Followed by ProQuad Control Group (Per-Protocol Analysis)**

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

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
† Estimated responses and their fold-difference were based on statistical analysis models adjusting for study center and prevaccination titer.
‡ ProQuad + PCV7 / PCV7 followed by ProQuad.
The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5, (*i.e.*, excluding a decrease of 2-fold or more). This indicates that the fold-difference is statistically significantly less than the pre-specified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.
N = Number of subjects vaccinated in each treatment group; n = Number of subjects contributing to the per-protocol analysis for the given serotype; GMT = geometric mean titer; CI = Confidence interval.

In a clinical trial, 653 healthy children 12 to 15 months of age were randomized to receive VAQTA, ProQuad, and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA 6 weeks later (N=323) *[see Adverse Reactions (6.1) for ethnicity and gender information].* Statistical analysis of non-inferiority of the response rate for varicella antibody at 6 weeks postvaccination among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 15. For the varicella component of ProQuad, in subjects with baseline antibody titers <1.25 gpELISA units/mL, the proportion with a titer ≥5 gpELISA units/mL 6 weeks after their first dose of ProQuad was non-inferior when ProQuad was administered with VAQTA and pneumococcal 7-valent conjugate vaccine as compared to the proportion with a titer ≥5 gpELISA units/mL when ProQuad was administered with pneumococcal 7-valent conjugate vaccine alone. Statistical analysis of non-inferiority of the seropositivity rate for hepatitis A antibody at 4 weeks postdose 2 of VAQTA among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 16. The seropositivity rate to hepatitis A 4 weeks after a second dose of VAQTA given concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine (defined as the percent of subjects with a titer ≥10 mIU/mL) was non-inferior to the seropositivity rate observed when VAQTA was administered separately from ProQuad and pneumococcal 7-valent conjugate vaccine. Statistical analysis of non-inferiority in GMT to *S. pneumoniae* serotypes at 6 weeks postvaccination among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 17. Additionally, the GMTs for *S.*

*pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after vaccination with pneumococcal 7-valent conjugate vaccine administered concomitantly with ProQuad and VAQTA were non-inferior as compared to GMTs observed in the group given pneumococcal 7-valent conjugate vaccine with ProQuad alone. An earlier clinical study involving 617 healthy children provided data that indicated that the seroresponse rates 6 weeks post vaccination for measles, mumps, and rubella in those given M-M-R II and VAQTA concomitantly (N=309) were non-inferior as compared to historical controls.

**Table 15: Statistical Analysis of Non-Inferiority of the Response Rate for Varicella Antibody at 6 Weeks Postvaccination Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)**

| Parameter | Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330) | | Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323) | | Difference† (percentage points): Group 1 – Group 2 (95% CI) |
|---|---|---|---|---|---|
| | n | Estimated Response† | n | Estimated Response† | |
| % ≥5 gpELISA units/mL‡ | 225§ | 93.2% | 232§ | 98.3% | -5.1 (-9.3, -1.4) |

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for varicella; CI = Confidence interval.
† Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.
‡ 6 weeks following Dose 1.
§ Initial Serostatus <1.25 gpELISA units/ mL.
The conclusion of similarity (non-inferiority) was based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease of 10 percentage points or more (lower bound >-10.0). This indicated that the risk difference was statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.

**Table 16: Statistical Analysis of Non-Inferiority of the Seropositivity Rate (SPR) for Hepatitis A Antibody at 4 Weeks Postdose 2 of VAQTA Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)**

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

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

**Table 17: Statistical Analysis of Non-Inferiority in Geometric Mean Titers (GMT) to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)**

| Serotype | Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330) | | Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323) | | Fold-Difference† (95% CI) |
|---|---|---|---|---|---|
| | n | Estimated Response† | n | Estimated Response† | |

| | | | | | |
|---|---|---|---|---|---|
| 4 | 246 | 1.9 | 247 | 1.7 | 1.1 (0.9, 1.3) |
| 6B | 246 | 9.9 | 246 | 9.9 | 1.0 (0.8, 1.2) |
| 9V | 247 | 3.7 | 247 | 4.2 | 0.9 (0.8, 1.0) |
| 14 | 248 | 7.8 | 247 | 7.6 | 1.0 (0.9, 1.2) |
| 18C | 247 | 2.9 | 247 | 2.7 | 1.1 (0.9, 1.3) |
| 19F | 248 | 4.0 | 248 | 3.8 | 1.1 (0.9, 1.2) |
| 23F | 247 | 5.1 | 247 | 4.4 | 1.1 (1.0, 1.3) |

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

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

In a clinical trial, 1913 healthy children 12 to 15 months of age were randomized to receive ProQuad plus diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine concomitantly at separate injection sites (N=949), ProQuad at the initial visit followed by DTaP and *Haemophilus* b conjugate and hepatitis B (recombinant) vaccine given concomitantly 6 weeks later (N=485), or M-M-R II and VARIVAX given concomitantly at separate injection sites (N=479) at the first visit *[see Adverse Reactions (6.1) for ethnicity and gender information].* Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, anti-PRP, and hepatitis B were comparable between the 2 groups given ProQuad at approximately 6 weeks postvaccination indicating that ProQuad and *Haemophilus* b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine may be administered concomitantly at separate injection sites (see Table 18 below). Response rates for measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, and hepatitis B were not inferior in children given ProQuad plus *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines concomitantly when compared to ProQuad at the initial visit and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines given concomitantly 6 weeks later. There are insufficient data to support concomitant vaccination with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (data not shown).

**Table 18: Summary of the Comparison of the Immunogenicity Endpoints for Measles, Mumps, Rubella, Varicella, *Haemophilus influenzae* type b, and Hepatitis B Responses Following Vaccination with ProQuad, *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant) Vaccine and DTaP Administered Concomitantly Versus Non-Concomitant Vaccination with ProQuad Followed by These Vaccines**

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

| | | | | | |
|---|---|---|---|---|---|
| | | | | (-4.8, -0.8) | |

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

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4171 — ProQuad is supplied as follows:

(1) a package of 10 single-dose vials of lyophilized vaccine, NDC 0006-4171-00 (package A)

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

*Storage*

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

**Before reconstitution, store the lyophilized vaccine in a freezer at a temperature between −58°F and +5°F (−50°C and −15°C) for up to 18 months. Any freezer (*e.g.*, chest, frost-free) that reliably maintains an average temperature between −58°F and +5°F (−50°C and −15°C) and has a separate sealed freezer door is acceptable for storing ProQuad. Routine defrost cycling of a frost-free freezer is acceptable.**

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

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

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

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

**DO NOT FREEZE RECONSTITUTED VACCINE.**

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

**For information regarding the product or questions regarding storage conditions, call 1-800-MERCK-90.**

## 17 PATIENT COUNSELING INFORMATION

*Instructions*

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

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

Inform the patient, parent, or guardian that the vaccine recipient should avoid use of salicylates for 6 weeks after vaccination with ProQuad *[see Warnings and Precautions (5.8) and Drug Interactions (7.2)]*.

Instruct postpubertal females to avoid pregnancy for 3 months following vaccination *[see Indications and Usage (1), Contraindications (4.5) 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 www.vaers.hhs.gov.

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