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ProQuad®

[Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live] Refrigerator-stable formulation

DESCRIPTION

ProQuad* is a combined attenuated live virus vaccine containing measles, mumps, rubella, and varicella viruses. ProQuad is a sterile lyophilized preparation of (1) the components of M-M-R*II (Measles, Mumps and Rubella Virus Vaccine Live): 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) refrigerator-stable formulation, 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 preparation for subcutaneous administration. Each 0.5-mL dose contains not less than 3.00 $\log_{10}$ $TCID_{50}$ (50% tissue culture infectious dose) of measles virus; 4.30 $\log_{10}$ $TCID_{50}$ of mumps virus; 3.00 $\log_{10}$ $TCID_{50}$ of rubella virus; and a minimum of 3.99 $\log_{10}$ PFU (plaque-forming units) of Oka/Merck varicella virus.

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, 1.4 mg of sodium phosphate, 0.25 mg of human albumin, 0.13 mg of sodium bicarbonate,94 mcg of potassium phosphate, 58 mcg of potassium chloride; residual components of MRC-5 cells including DNA and protein; 5 mcg of neomycin, bovine serum albumin (0.5 mcg), and other buffer and media ingredients. The product contains no preservative.

CLINICAL PHARMACOLOGY

Background

Measles, mumps, rubella, and varicella are 4 common childhood diseases caused by measles virus, mumps virus, rubella virus, and varicella virus, respectively. These diseases may be associated with serious complications and/or death. For example, measles can be associated with pneumonia and encephalitis; mumps can be associated with aseptic meningitis, deafness, and orchitis; rubella occurring during pregnancy can cause congenital rubella syndrome in the infants of infected mothers; and wild-type varicella can be associated with bacterial superinfection, pneumonia, encephalitis, and Reye's syndrome.

Mechanism of action

In clinical efficacy studies, seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases. Also, in previous studies with varicella vaccine, antibody responses against varicella virus ≥5 units/mL in a glycoprotein enzyme-linked immunosorbent assay (gpELISA) (not commercially available) similarly correlated with long-term protection. 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) and seroresponse rates for varicella virus were similar to those observed after vaccination with a single dose of VARIVAX (see CLINICAL STUDIES). The duration of protection from measles, mumps, rubella, and varicella infections after vaccination with ProQuad is unknown.

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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.[1] Varicella antibodies were present for up to ten years post-vaccination in most of the individuals tested who received 1 dose of VARIVAX.

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.[2-9]

Immunogenicity

Immunogenicity was studied in 7364 healthy children 12 months through 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 the frozen formulation of ProQuad was similar to that of its individual component vaccines (M-M-R II and VARIVAX). The immunogenicities of the refrigerator-stable formulation and 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.

Children who received a single dose of ProQuad at 12 through 23 months of age

In 4 randomized clinical trials, 5446 healthy children 12 through 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 *Studies With Other Vaccines*), no concomitant vaccines were permitted during study participation. Following a single dose of ProQuad, the vaccine response rates were 97.4% (95% CI: 96.9, 97.9) for measles, 95.8 (95% CI: 95.1, 96.4) to 98.8% (95% CI: 97.9, 99.4) for mumps, and 98.5% (95% CI: 98.1, 98.8) for rubella. The vaccine response rate was 91.2% (95% CI: 90.3, 92.0) for varicella. 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. Fever and measles-like rashes were the only adverse experiences that occurred more frequently in recipients of a single dose of ProQuad compared with recipients of single doses of M-M-R II and VARIVAX (see ADVERSE REACTIONS).

In an additional clinical study, 1519 children 12 through 23 months of age received either the refrigerator-stable formulation of ProQuad (N=1006) or the frozen formulation of ProQuad (N=513). Subjects enrolled in this trial had a negative clinical history, no known recent exposure, and no vaccination history of measles, mumps, rubella, and varicella. Children were excluded from study participation if they had an immune impairment or had a history of allergy to components of the vaccine. No concomitant vaccines were permitted during the study participation. Following a single dose of the

refrigerator-stable formulation of ProQuad, the vaccine response rates were 99.1% (95%CI: 98.2, 99.6) for measles, 97.7% (95% CI: 96.5, 98.6) for mumps, and 99.6% (95% CI: 98.9, 99.9) for rubella. The vaccine response rate was 90.1% (95% CI: 87.9, 92.0) for varicella. The results were similar to the immune response rates induced by the frozen formulation of ProQuad in the same study. The refrigerator-stable formulation of ProQuad was generally well tolerated. The safety profile of the refrigerator-stable formulation of ProQuad was comparable to that of the frozen formulation of ProQuad (see ADVERSE REACTIONS).

Children Who Received a Second Dose of ProQuad

In 2 clinical trials[10-11], 1035 children were administered a second dose of ProQuad approximately 3 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 proportion of initially seronegative vaccinees with positive serological responses following two doses were 99.4% (95% CI: 98.6, 99.8) for measles, 99.9% (95% CI: 99.4, 100) for mumps, 98.3% (95% CI: 97.2, 99.0) for rubella, and 99.4% (95% CI: 98.7, 99.8) for varicella (≥5 gpELISA units/mL). 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.

In these trials, the rates of adverse experiences after the second dose of ProQuad were generally similar to, or lower than, those seen with the first dose. The fever rate was lower after the second dose than after the first dose.

Children Who Received ProQuad at 4 through 6 Years of Age After Primary Vaccination With M-M-R II and VARIVAX

In a clinical trial involving 799 healthy 4- through 6-year-old children who had received M-M-R II and VARIVAX at least 1 month prior to study entry, 399 received ProQuad and placebo while 205 received M-M-R II and placebo concomitantly at separate injection sites. Another 195 healthy children were administered M-M-R II and VARIVAX concomitantly at separate injection sites. 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.

Following the dose of ProQuad, seropositivity rates were 99.2% (95% CI: 97.6, 99.8) for measles, 99.5% (95% CI: 98.0, 99.9) for mumps, 100% (95% CI: 99.0, 100) for rubella, and 98.9% (95% CI: 97.2, 99.7) for varicella (≥5 gpELISA units/mL). Approximate geometric mean fold-rises in antibody titers (pre-vaccination to post-vaccination) for measles, mumps, rubella, and varicella were 1.2, 2.4, 3.0 and 12, respectively. Post-vaccination GMTs for recipients of ProQuad were similar to those following a second dose of M-M-R II and VARIVAX administered concomitantly at separate injection sites. 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 rates of adverse experiences, including the most commonly reported adverse experiences of injection site reactions, nasopharyngitis and cough were generally similar among the 3 treatment groups.

Studies With Other Vaccines

In a clinical trial involving 1913 healthy children 12 through 15 months of age, 949 received 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. Another 485 healthy children received ProQuad at the initial visit followed by DTaP and *Haemophilus* b Conjugate and Hepatitis B (Recombinant) Vaccine given concomitantly 6 weeks later while 479 children were immunized with M-M-R II and VARIVAX given concomitantly at separate injection sites at the first visit. Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, anti-PRP and hepatitis B were comparable between the 2 groups at approximately 6 weeks post-vaccination indicating the ProQuad and *Haemophilus* b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine may be administered concomitantly at separate injection sites. There are insufficient data to support concomitant immunization

with diphtheria, tetanus and acellular pertussis vaccine. No clinically significant differences in adverse experiences were reported between treatment groups.

Herpes Zoster

Two cases of herpes zoster were reported in 2108 healthy subjects 12 through 23 months of age who were vaccinated with ProQuad in clinical trials and followed for 1 year. Both cases were unremarkable and no sequelae were reported (see ADVERSE REACTIONS, *Other*).

Reye's Syndrome

Reye's syndrome following wild-type varicella infection has occurred in children and adolescents, the majority of whom had received salicylates. In 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.

INDICATIONS AND USAGE

ProQuad is indicated for vaccination against measles, mumps, rubella, and varicella in children 12 months through 12 years of age.

ProQuad may also be used in children 12 months through 12 years of age if a second dose of measles, mumps and rubella vaccine is to be administered.

CONTRAINDICATIONS

ProQuad should not be administered:

- 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.
- to individuals with a history of hypersensitivity to gelatin or any other component of the vaccine (see WARNINGS for exceptions).
- to individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system.
- to individuals on immunosuppressive therapy (including high-dose systemic corticosteroids); 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.
- 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.[12]
- to individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.
- to individuals with active untreated tuberculosis.
- to individuals with an active febrile illness with fever >101.3°F (>38.5°C).
- to individuals who are pregnant; the possible effects of the vaccine on fetal development are unknown at this time (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Caution should be exercised in 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. The physician should be alert to the temperature elevations that may occur following vaccination (see ADVERSE REACTIONS). 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.

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. The potential risk-to-benefit ratio should be carefully evaluated 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 PRECAUTIONS).[13]

Children with egg allergy are at low risk for anaphylactic reactions to measles-containing vaccines (including MMR), and skin testing of children allergic to eggs is not predictive of reactions to MMR vaccine. Persons with allergies to chickens or feathers are not at increased risk of reaction to the vaccine.[10]

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.

Thrombocytopenia

No clinical data are available regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad. 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. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination with ProQuad in such cases.

Theoretical Risk of Transmission of Creutzfeldt-Jakob Disease

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.

PRECAUTIONS

General

Prior to administering the vaccine, obtain the prospective vaccinee's vaccination history and determine whether the individual had any previous reactions to any vaccine including ProQuad, VARIVAX or any measles-, mumps-, or rubella-containing vaccines.

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic reaction occur.

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 doses of corticosteroids.

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

The safety and efficacy of ProQuad for use in children and young adults who are known to be infected with human immunodeficiency viruses have not been established (see CONTRAINDICATIONS).

Transmission

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk. However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see PRECAUTIONS, *Nursing Mothers*).

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

Post-licensing experience with VARIVAX suggests that transmission of varicella vaccine virus may occur rarely between healthy vaccine recipients who 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.

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.

Information for Patients

The health care provider should provide the required vaccine information to the patient, parent, or guardian.

The health care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination.

The health care provider should tell the vaccine recipient or his or her parent or guardian that the vaccine recipient should avoid use of salicylates for 6 weeks after vaccination with ProQuad (see DRUG INTERACTIONS).

Female vaccine recipients of childbearing age should be told to avoid pregnancy for 3 months following vaccination.

Patients, parents, or guardians should be told that vaccination with ProQuad may not offer 100% protection from measles, mumps, rubella, and varicella infection.

Patients, parents, or guardians should be instructed 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. The VAERS toll-free number for VAERS forms and information is 1-800-822-7967 or information may be submitted electronically via http://www.fda.gov/cber/vaers/vaers.htm

Drug Interactions

Immune Globulins and Transfusions

Immune globulins administered concomitantly with ProQuad may interfere with the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of immune globulins (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]).[13] Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination.[13]

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.

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.

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.

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. If for any reason a second dose of varicella-containing vaccine is required, at least 3 months should elapse between administration of the 2 doses.

ProQuad may be administered concomitantly with *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine.

There are no data regarding the administration of ProQuad with inactivated poliovirus vaccine or pneumococcal conjugate vaccine.

There are insufficient data to support concomitant vaccination with diphtheria, tetanus and acellular pertussis vaccine (see CLINICAL STUDIES, *Studies with Other Vaccines*).

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.

Carcinogenesis, Mutagenesis, Teratogenicity, Impairment of Fertility

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

Pregnancy

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

It is also not known whether ProQuad can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, ProQuad should not be administered to pregnant females. If vaccination of post-pubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination (see CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to natural 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;[14] (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;[15] and (4) Wild-type varicella can sometimes cause congenital varicella infection.

Merck & Co., Inc. maintains a Pregnancy Registry to monitor fetal outcomes in 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.

Nursing Mothers

The secretion of viruses in human milk has not been studied in measles and mumps vaccine viruses. 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.[16-17] For additional information on transmission of vaccine virus from vaccine recipients to susceptible infants, see *Transmission*. ProQuad should not be administered to nursing women.

Pediatric Use

No clinical data are available on the safety, immunogenicity, and efficacy of ProQuad in children less than 12 months of age.

Geriatric Use

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

ADVERSE REACTIONS

Children 12 through 23 Months of Age

ProQuad frozen or ProQuad refrigerator-stable formulation was administered to 6038 children 12 through 23 months of age in 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 at separate injection sites. The safety profile for ProQuad was similar to that of the component vaccines.

The only systemic vaccine-related adverse experiences that were reported at a significantly greater rate in individuals who received ProQuad than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites were fever (≥102°F [≥38.9°C] oral equivalent or abnormal) (21.5% versus 14.9%, respectively), and measles-like rash (3.0% versus 2.1%, respectively). Both fever and measles-like rash usually occurred within 5 to 12 days following the vaccination, were of short duration, and resolved with no long-term sequelae. Pain/tenderness/soreness at the injection site was reported at a statistically lower rate in individuals who received ProQuad than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites (22.0% versus 26.7%, respectively). The only vaccine-related injection-site adverse experience that was more frequent among recipients of ProQuad than recipients of M-M-R II and VARIVAX was rash at the injection site (2.3% versus 1.5%, respectively). Table 1 summarizes the frequencies of injection-site and systemic adverse experiences that were reported as vaccine related by the investigator among ≥1% of children in randomized, blinded clinical trials performed prior to licensure that were designed to compare ProQuad frozen versus M-M-R II and VARIVAX.

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

Adverse Experiences	ProQuad (frozen) (N = 4497) %	M-M-R II and VARIVAX (N = 2038) %
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 ≥102°F (≥38.9°C)[‡§]	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 experiences for M-M-R II and VARIVAX are based on occurrence with either of the vaccines administered.
‡ Designates a solicited adverse experience. Injection-site adverse experiences were solicited only from Days 0-4 postvaccination.
§ Temperature reported as oral equivalent or abnormal.

Clinical safety of the refrigerator-stable formulation of ProQuad (n=983) was compared with that of the licensed frozen formulation of ProQuad (n=500) for 42 days postvaccination in children 12 through 23 months of age. The safety profiles were comparable for the two different formulations. Pain/tenderness/soreness (29.6% vs. 30.4%) and erythema (17.8% vs. 18.0%) were the most commonly reported injection site reactions in recipients of the refrigerator-stable and frozen formulations of ProQuad, respectively. The most common systemic adverse reactions (reported by >10% of subjects in one or more treatment groups, irrespective of causal relationship to vaccination) were: diarrhea (11.2% vs. 9.2%), fever (17.1% vs. 17.2%), nasopharyngitis (14.1% vs. 15.8%), otitis media (15.0% vs. 15.2%), upper respiratory tract infection (19.9% vs. 20.8%), in children given the refrigerator-stable and frozen formulations of ProQuad, respectively. Nine subjects reported serious adverse reactions (7 following administration of the refrigerator-stable formulation and two after the frozen formulation of ProQuad); all were judged by the investigators as being unrelated to vaccination.

Across clinical studies (N=6038), the following vaccine-related clinical adverse experiences (incidence ≥0.2%) were observed in individuals following a single dose of ProQuad. Solicited adverse experiences are designated with the symbol (‡).

Infections and infestations: nasopharyngitis, otitis media, upper respiratory infection, viral infection.

Metabolism and nutrition disorders: anorexia.

Psychiatric disorders: insomnia, irritability, sleep disorder.

Nervous system disorders: somnolence.

Respiratory, thoracic, and mediastinal disorders: cough, nasal congestion, respiratory congestion, rhinorrhea.

Gastrointestinal disorders: diarrhea, vomiting.

Skin and subcutaneous tissue disorders: dermatitis (including contact, atopic, and diaper rash), eczema, measles-like rash‡, rash, rubella-like rash‡, varicella-like rash‡, viral exanthema.

General disorders and administration site conditions: fever, injection site ecchymosis or swelling‡, injection site erythema‡, injection site hemorrhage, injection site pain/tenderness/soreness‡, injection site rash‡, malaise.

Post-marketing reports

The following additional adverse events have been reported with ProQuad in post-marketing experience.

Infections and infestations: herpes zoster, varicella.

Immune system disorders: anaphylactic reaction.

Nervous system disorders: ataxia, convulsion, febrile seizure.

Skin and subcutaneous tissue disorders: pruritus.

Adverse Experiences after vaccination with M-M-R II or VARIVAX

The following additional adverse experiences have been reported in clinical studies and with marketed use of either M-M-R II, the monovalent component vaccines of M-M-R II, or VARIVAX. These adverse effects are listed below without regard to causality or frequency.

Infections and infestations

Atypical measles, candidiasis, cellulitis, infection, influenza, measles, orchitis, parotitis, respiratory infection, skin infection.

Blood and the lymphatic system disorders

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), Bell's palsy, cerebrovascular accident, dizziness, dream abnormality, encephalitis (see below), encephalopathy (see below), Guillain-Barré syndrome, headache, hypersomnia, measles inclusion body encephalitis (see CONTRAINDICATIONS), 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, pneumonitis (see CONTRAINDICATIONS), 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, 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.

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.

Post-marketing surveillance

The discussion that follows describes adverse reactions that have been identified post-approval for the monovalent components of ProQuad. Because these reactions are 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.

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals. 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.[18]

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. Post-marketing surveillance of the more than 400 million doses that have been distributed worldwide (1978 to 2003) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. 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).

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and gender, being greatest in

adult females and least in prepubertal children. Following vaccination in children, reactions in joints are generally uncommon (0 to 3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (12 to 26%), and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and adult women. In women 35 to 45 years old these reactions are generally well tolerated and rarely interfere with normal activities.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated measles vaccine distribution in the United States (US), the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6 to 22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study 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.

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.[19] 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.

DOSAGE AND ADMINISTRATION

Dosage

When reconstituted, each vial of ProQuad contains a single 0.5-mL dose. Individuals 12 months through 12 years of age should receive a single 0.5-mL dose of ProQuad administered subcutaneously. 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. If for any reason a second dose of varicella-containing vaccine is required, at least 3 months should elapse between administration of the 2 doses.

Preparation

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.

Visually inspect the vaccine before and after reconstitution for particulate matter and discoloration 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. DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

ProQuad®
[Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live] 9763402
Refrigerator-stable formulation

Method of Administration
FOR SUBCUTANEOUS ADMINISTRATION
DO NOT INJECT INTRAVASCULARLY

Use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one individual to another.

The vaccine is to be injected subcutaneously in the outer aspect of the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Properly dispose of all needles and syringes. Do not recap needles.

Use With Other Vaccines

If another vaccine is administered concomitantly, a different injection site should be used.

See PRECAUTIONS, *Drug Interactions, Use With Other Vaccines*.

HOW SUPPLIED

No. 4993 — ProQuad is supplied as follows: (1) a package of 10 single-dose vials of lyophilized vaccine, **NDC** 0006-4993-41 (package A); and (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.

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).

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