

## **Informasi Untuk Pasien Tentang ProQuad**

**[Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live]**

**Refrigerator-stable formulation**

### **Apa ProQuad?**

ProQuad (Measles, Mumps, Rubella dan Varicella [Oka / Merck] Virus Vaksin Hidup, MSD) adalah vaksin virus injeksi untuk membantu mencegah campak (rubeola), mumps, rubella (campak Jerman), dan varicella (cacar air).

Pemegang Izin Produk :

PT Merck Sharp Dohme Pharma Tbk

Pasuruan, Jawa Timur

Produsen:

Merck Sharp & Dohme Corp.,

West Point, PA 19486, USA

Dikemas & dirilis oleh:

Merck Sharp & Dohme B.V.

Haarlem, Netherlands

### **Mengapa dokter saya meresepkan ProQuad?**

Dokter merekomendasikan atau memberikan ProQuad untuk membantu melindungi anak Anda terhadap campak, gondok, rubella, dan varicella. Vaksin ini dapat diberikan kepada anak 12 bulan hingga 23 bulan.

Campak (rubeola) adalah penyakit menular yang serius yang sangat mudah ditularkan dari satu orang ke orang lain. Campak menyebabkan demam tinggi, batuk, dan ruam dan berlangsung selama 1 sampai 2 minggu. Satu dari setiap 10 anak-anak yang terkena campak juga akan



mengalami infeksi telinga atau pneumonia. Pada kejadian langka, campak juga dapat menyebabkan infeksi otak yang dapat menyebabkan kejang, gangguan pendengaran, retardasi mental, dan bahkan kematian. Bayi dan orang dewasa yang terkena campak sering jauh lebih sakit untuk waktu yang lama atau lebih mungkin meninggal dibandingkan anak-anak dan remaja yang terkena campak.

Gondong adalah penyakit menular yang mudah ditularkan dari satu orang ke orang lain dan menyebabkan demam, sakit kepala, dan bengkak, kelenjar menyakitkan di bawah rahang (kelenjar ludah). Kadang-kadang bisa menjadi penyakit yang sangat serius dan biasanya berlangsung selama beberapa hari. Gondok dapat menyebabkan peradangan ringan pada otak dan sumsum tulang belakang (meningitis) pada sekitar 1 orang di setiap 10 orang yang terkena. Sekitar 1 dari setiap 4 laki-laki remaja atau orang dewasa dengan gondongan akan memiliki pembengkakan yang menyakitkan pada testis selama beberapa hari (ini biasanya tidak mempengaruhi kemampuannya pada saat dewasa). Remaja dan orang dewasa, terutama laki-laki, yang menangkap gondok sering jauh lebih sakit dan lebih mungkin untuk menderita lebih lama dari anak-anak.

Rubella (campak Jerman) biasanya merupakan penyakit ringan yang menyebabkan demam ringan, pembengkakan kelenjar di leher, nyeri dan pembengkakan pada sendi, dan ruam yang berlangsung untuk waktu yang singkat tetapi sangat berbahaya jika terkena pada wanita hamil. Wanita yang terkena rubella saat hamil dapat memiliki bayi yang lahir mati, atau memiliki penyakit jantung, kebutaan, tuli, atau masalah dengan belajar.

Varicella (cacar air) adalah penyakit menular yang mudah ditularkan dari satu orang ke orang lain dan terjadi paling sering pada anak-anak 5 sampai 9 tahun. Hal ini terutama menyebar dari orang ke orang melalui udara melalui bersin atau batuk. Gejala varicella termasuk sakit kepala ringan, demam sedang, dan ketidaknyamanan umum. Ini diikuti dengan ruam gatal, bintik-bintik merah kecil yang biasanya mulai di dada, perut atau punggung, tetapi dapat muncul di manapun pada tubuh. Ada mungkin hanya beberapa tempat atau kelompok bintik-bintik, atau bahkan ratusan bintik-bintik yang berkembang selama 3 sampai 5 hari ke depan. Bintik-bintik akan berubah menjadi lepuh yang jelas berisi cairan yang kemudian menjadi berawan, pecah, kering, keropeng, dan menyembuhkan, biasanya dalam waktu 5 sampai 20 hari. Komplikasi yang paling umum adalah infeksi bakteri kulit. Kurang sering terjadi tetapi sangat serius

berusaha untuk menghindari kontak, hingga 6 minggu setelah vaksinasi, dengan orang-orang untuk siapa penyakit ini mungkin sangat serius. Orang-orang ini meliputi:

- individu dengan sistem kekebalan tubuh yang lemah
- ibu hamil yang pernah varicella
- bayi yang baru lahir yang ibunya pernah varicella

Beritahu dokter jika ada orang yang jatuh ke salah satu kategori di atas dan diharapkan berada dalam kontak dengan penerima vaksin.

ProQuad dapat digunakan untuk vaksinasi campak, gondok, rubella, dan varicella. Waktu yang tepat dan jumlah injeksi akan ditentukan oleh dokter Anda menggunakan rekomendasi resmi yang sesuai.

#### Penggunaan pada kehamilan.

ProQuad tidak boleh diberikan kepada wanita hamil. Wanita usia subur harus mengambil tindakan pencegahan yang diperlukan untuk menghindari kehamilan selama 3 bulan setelah vaksinasi.

#### Penggunaan selama menyusui.

Beritahu dokter jika penerima vaksin menyusui atau berniat untuk menyusui. Dokter Anda akan memutuskan apakah ProQuad harus diberikan.



#### Dapatkan anak saya divaksinasi dengan ProQuad dan vaksin lainnya pada saat yang sama?

Beritahu dokter jika anak Anda baru-baru ini menerima vaksin atau jika ada yang dijadwalkan akan diberikan dalam waktu dekat. Dokter akan menentukan kapan ProQuad dapat diberikan. Setidaknya 1 bulan harus berlalu antara dosis campak, gondok, dan vaksin rubella dan ProQuad. Jika untuk alasan apapun dosis kedua vaksin yang mengandung varicella diperlukan, minimal 1 bulan harus berlalu antara pemberian dosis.



komplikasi termasuk pneumonia, radang otak (ensefalitis), sindrom Reye (peradangan hati yang berhubungan dengan gangguan kesadaran), dan kematian. Penyakit berat dan komplikasi serius lebih mungkin terjadi pada remaja dan orang dewasa. Penyakit dan menyertai komplikasi dari varicella secara signifikan turun sejak pengenalan vaksin varicella pada tahun 1995.

**Apa yang harus saya ketahui sebelum vaksinasi dengan ProQuad?**

**Siapa yang tidak boleh divaksinasi dengan ProQuad?**

Setiap orang yang:

- Alergi terhadap salah satu komponennya (termasuk neomisin)
- Memiliki kelainan darah atau jenis kanker yang mempengaruhi sistem kekebalan tubuh (selain penggantian kortikosteroid)
- Menggunakan obat untuk menekan sistem kekebalan tubuh (selain penggantian kortikosteroid)
- Memiliki defisiensi imun akibat penyakit (seperti AIDS) atau pengobatan
- Memiliki TB yang tidak diobati aktif
- Demam lebih tinggi dari 38,5° C (lebih tinggi dari 101,3° F); Namun, demam rendah bukanlah alasan untuk menunda vaksinasi
- Hamil (di samping itu, kehamilan harus dihindari selama 3 bulan setelah vaksinasi)

**Apa yang harus dokter diberitahu sebelum anak saya divaksinasi dengan ProQuad?**

Beritahu dokter tentang masalah kesehatan anak Anda memiliki atau telah memiliki, dan tentang segala alergi (terutama untuk neomisin).

Beritahu dokter jika anak Anda memiliki riwayat kejang atau cedera otak, jumlah platelet darah yang rendah, atau telah menerima darah atau plasma transfusi atau administrasi globulin serum manusia dalam 3 bulan terakhir.

The Oka / Merck strain virus varicella telah terbukti ditularkan dari penerima vaksin varicella untuk orang-orang di risiko terkena varicella, meskipun hal ini jarang terjadi. Ini strain virus varicella adalah di ProQuad. Bila mungkin, orang yang telah divaksinasi dengan ProQuad harus



Dokter mungkin menunda vaksinasi selama 3 bulan atau lebih setelah darah atau plasma transfusi, atau administrasi globulin imun normal manusia (IG), atau varicella zoster immune globulin (VZIG).

*Dapatkan anak saya menjalani tes medis dengan ProQuad?*

Jika tes tuberkulin yang akan dilakukan, itu harus dilakukan baik setiap saat sebelum, bersamaan dengan, atau 4 sampai 6 minggu setelah vaksinasi dengan ProQuad.

*Dapatkan anak saya divaksinasi dengan ProQuad dan menerima obat-obatan lainnya pada saat yang sama?*

Penggunaan salisilat (misalnya, asam asetilsalisilat atau aspirin) harus dihindari selama 6 minggu setelah vaksinasi dengan ProQuad karena penggunaan salisilat selama infeksi varicella alam telah dikaitkan dengan sindrom Reye (lihat Mengapa dokter diresepkan ProQuad?).

*Dapatkan penerima vaksin mengemudi atau mengoperasikan mesin setelah vaksinasi dengan ProQuad?*

Tidak ada informasi yang menunjukkan bahwa ProQuad mempengaruhi kemampuan vaksin penerima untuk mengemudi atau mengoperasikan mesin.

*Informasi tentang bahan-bahan aktif di ProQuad.*



ProQuad mengandung gelatin dan sejumlah jejak neomycin sebagai bahan aktif. Beritahu dokter jika anak Anda pernah memiliki reaksi alergi terhadap bahan ini.

*Apa jadwal vaksinasi untuk ProQuad?*

ProQuad diberikan melalui suntikan kepada orang 12 bulan hingga 23 bulan. Jika dosis kedua dari campak yang mengandung vaksin diperlukan, maka ProQuad dapat digunakan untuk dosis ini. Waktu yang tepat dan jumlah injeksi akan ditentukan oleh dokter Anda menggunakan rekomendasi resmi yang sesuai.

Berbicara dengan dokter untuk lebih jelasnya.

*Apa yang harus saya lakukan jika saya melewatkan dosis?*

Dokter Anda akan memutuskan kapan untuk memberikan dosis terjawab.

*Apa efek yang tidak diinginkan mungkin ProQuad miliki?*

Seperti semua obat-obatan, ProQuad dapat memiliki efek samping.

Efek samping yang paling umum dilaporkan dengan penggunaan ProQuad adalah: keluhan tempat suntikan termasuk nyeri / nyeri tekan / nyeri, kemerahan, bengkak atau memar; demam (38,9 ° C atau lebih tinggi); iritabilitas; ruam (termasuk campak seperti ruam, varicella seperti ruam, eksantema virus, dan injeksi situs ruam); infeksi saluran pernapasan atas; muntah dan diare.

Efek samping lain yang kurang umum telah dilaporkan administrasi berikut ProQuad, dan beberapa dari mereka serius. Ini termasuk: reaksi alergi (gatal-gatal); kejang demam; batuk dan bronchiolitis; dan kegoyangan dengan berjalan kaki.

Efek samping lainnya telah dilaporkan dengan penggunaan minimal salah satu dari berikut: ProQuad, MMR II, komponen monovalen MMR II, atau Varivax. Maskapai efek samping termasuk memar lebih mudah dari biasanya; merah atau ungu, datar, bintik-bintik kepala peniti di bawah kulit; pucat parah; perdarahan yang tidak biasa atau memar di bawah kulit; pembengkakan testis; kesemutan kulit; herpes zoster (shingles); radang otak (ensefalitis); gangguan kulit yang parah; infeksi kulit; Stroke; kejang tanpa demam; nyeri sendi dan / atau pembengkakan (yang bisa bersifat sementara atau kronis); radang paru-paru (pneumonia / pneumonitis); dan varicella (cacar air).

Dokter memiliki daftar yang lebih lengkap dari efek samping untuk ProQuad dan untuk komponen vaksin untuk ProQuad (MMR II dan Varivax).



Beritahu dokter segera tentang salah satu atau gejala yang tidak biasa lainnya. Jika kondisi tersebut terus berlangsung atau memburuk, mencari perhatian medis.

Cara mempelajari lebih lanjut tentang ProQuad (dan kondisi yang diresepkan):

Tidak semua informasi tentang vaksin ini dicetak di sini. Jika Anda memiliki pertanyaan tambahan, meminta dokter yang memiliki informasi resep penuh.

MENGANDUNG BABI

HARUS DENGAN RESEP DOKTER

**Registration No.**

Box, 1 vial @ 0,5 mL + 1 vial of diluent – Reg No. DKIXXXXXXXXXX

Batas kadaluarsa: 18 bulan

Setelah rekonstitusi dapat disimpan sampai 30 menit

PIL Version 1.1

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## **ProQuad**

**[Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live]**

**Refrigerator-stable formulation**

### **1. THERAPEUTIC CLASS**

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), the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells (hereafter referred to as VARIVAX).

### **2. INDICATIONS**

ProQuad is indicated for vaccination against measles, mumps, rubella, and varicella in individuals 12 - 23 months of age.

### **3. DOSAGE AND ADMINISTRATION**

#### *Dosage*

Individuals 12 - 23 months of age should receive a single dose of ProQuad administered subcutaneously.



Do not give immune globulin (IG) or Varicella Zoster Immune Globulin (VZIG) concomitantly with ProQuad (see DRUG INTERACTIONS).

*Method of Administration*

FOR SUBCUTANEOUS ADMINISTRATION. DO NOT INJECT INTRAVASCULARLY.

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

CAUTION: A sterile syringe free of preservatives, antiseptics, detergents, and other antiviral substances must be used for each injection and/or reconstitution of ProQuad because these substances may inactivate the vaccine viruses.

To reconstitute the vaccine, use only the diluent supplied because it is free of preservatives or other antiviral substances, which might inactivate the vaccine viruses.

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

Withdraw the entire volume of solvent into a syringe (if a prefilled syringe is available, this step is not necessary). Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely. Withdraw the entire content of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

**IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Before reconstitution, the lyophilized vaccine is a white to pale yellow compact crystalline plug. ProQuad, when reconstituted, is a clear pale yellow to light pink liquid.



#### 4. CONTRAINDICATIONS

History of hypersensitivity to any component of the vaccine, including gelatin.

History of anaphylactoid reaction to neomycin.

Blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system.

Immunosuppressive therapy (including high-dose corticosteroids); however, ProQuad is not contraindicated for use in individuals who are receiving topical corticosteroids or low-dose corticosteroids, as are commonly used for asthma prophylaxis or in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease. Vaccination with a live attenuated vaccine, such as varicella, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals.

Primary and acquired immunodeficiency states, including immunosuppression in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis, pneumonitis, and death as a direct consequence of disseminated measles vaccine virus infection have been reported in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Active untreated tuberculosis.

Any active febrile illness with fever  $>38.5^{\circ}\text{C}$  ( $>101.3^{\circ}\text{F}$ ), however, low-grade fever itself is not a contraindication to vaccination.





Pregnancy; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. (See **PREGNANCY**.)

## 5. PRECAUTIONS

### *General*

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

Due caution should be employed in administration of ProQuad to persons with individual or family history of convulsions, a history of cerebral injury or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation that may occur following vaccination (see **SIDE EFFECTS**).

The safety and efficacy of ProQuad have not been established in individuals who are known to be infected with human immunodeficiency viruses with or without evidence of immunosuppression (see **CONTRAINDICATIONS**).

The duration of protection from measles, mumps, rubella, and varicella infection after vaccination with ProQuad is unknown (see **CLINICAL PHARMACOLOGY**).

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

### *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 **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 or do not develop a varicella-like rash) and contacts susceptible to varicella, as well as high-risk individuals susceptible to varicella.

High-risk individuals susceptible to varicella include:

- Immunocompromised individuals (see **CONTRAINDICATIONS**);
- Pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection;
- Newborn infants of mothers without documented positive history of varicella or laboratory evidence of prior infection.

Vaccine recipients should attempt to avoid, whenever possible, close association with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination. In circumstances where contact with high-risk individuals susceptible to varicella is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus.



#### *Hypersensitivity to Eggs*

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur.

### *Thrombocytopenia*

No clinical data are available regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad. Cases of thrombocytopenia have been reported in post-marketing experience after primary vaccination with ProQuad. In addition, cases of thrombocytopenia have been reported after primary vaccination or revaccination with measles vaccine; with measles, mumps, and rubella vaccine; and with varicella vaccine. Post-marketing experience with live measles, mumps, and rubella vaccine indicates that individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia following the first dose of a live measles, mumps, and rubella vaccine may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination with ProQuad in such cases (see **SIDE EFFECTS**).

### *Febrile seizures*

In the 5- to 12-day timeframe after the administration of the first dose of quadrivalent measles, mumps, rubella and varicella vaccines in children, an increased risk of febrile seizure was observed compared to concomitant administration of measles, mumps, rubella and varicella vaccines.

### *Post-Exposure Prophylaxis*

#### **Post Exposure Prophylaxis**

The safety and efficacy of ProQuad for use after exposure to measles, mumps, rubella, or varicella have not been established. No clinical data are available for ProQuad administered after exposure to measles, mumps, rubella, or varicella.

### *Females of Childbearing Age*

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

### *Adolescents and Adults*





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

#### *Tuberculin Test*

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

#### *Tuberculosis*

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.

#### *Albumin*

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

## **6. PREGNANCY**

Studies have not been conducted with ProQuad in pregnant women. It is also not known whether ProQuad can cause harm to the fetus when administered to a pregnant woman or can affect reproduction capacity. Therefore, ProQuad should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see **INDICATIONS, CONTRAINDICATIONS, and PRECAUTIONS**).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to wild-type measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to





assume that the vaccine strain of virus is also capable of inducing adverse fetal effects; (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans; (3) In a 15-year survey involving over 1100 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 635 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome; and (4) Wild-type varicella can sometimes cause harm to the fetus.

## **7. NURSING MOTHERS**

It is not known whether measles, mumps, or varicella virus is secreted in human milk. Studies have shown that lactating postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants who developed serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Therefore, caution should be exercised if ProQuad is inadvertently administered to a nursing woman.

## **8. PEDIATRIC USE**

ProQuad has not been studied in infants less than 12 months of age and is not recommended for administration in this age group.

## **9. DRUG INTERACTIONS**

At least 1 month should elapse between a dose of M-M-R II and a dose of ProQuad. If for any reason a second dose of varicella-containing vaccine is required, at least 1 month should elapse between administration of the 2 doses.

Administration of immune globulins (IG) concomitantly with ProQuad may interfere with the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of IG. However, the appropriate suggested



interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (e.g., 5 months for VZIG).

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

Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection.

The fourth dose of DTaP (diphtheria, tetanus, acellular pertussis vaccine) is indicated for children 15 months of age and older. Limited data suggest that ProQuad may be administered concomitantly (at separate injection sites) with DTaP in children 15 months of age and older (for children less than 15 months of age see **CLINICAL PHARMACOLOGY**).

Results from clinical studies indicate that ProQuad may be administered concomitantly with *Haemophilus b* conjugate (meningococcal protein conjugate), hepatitis B (recombinant), pneumococcal conjugate, and hepatitis A (inactivated) vaccines.

There are no data for the administration of ProQuad with inactivated poliovirus vaccine.

## 10. SIDE EFFECTS

### *Children 12 through 23 months of age*

In clinical trials, ProQuad was administered alone to 6038 children 12 through 23 months of age. ProQuad was generally well tolerated.

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



The only systemic vaccine-related adverse experiences that were reported at a significantly greater rate in individuals who received ProQuad than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites were fever ( $\geq 38.9^{\circ}\text{C}$  [ $\geq 102^{\circ}\text{F}$ ] 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).

Across clinical studies, the following adverse experiences were reported as vaccine-related by the investigator in individuals after a single dose of ProQuad (excluding single events with a frequency  $\leq 0.02\%$ ). Several adverse experiences were solicited in the clinical studies and are designated with the symbol (†).

[*Very common* ( $\geq 1/10$ ); *Common* ( $\geq 1/100$ ,  $<1/10$ ); *Uncommon* ( $\geq 1/1000$ ,  $<1/100$ ); *Rare* ( $\geq 1/10,000$ ,  $<1/1000$ )]

#### *Infections and infestations*

*Common:* upper respiratory infection

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

*Rare:* bronchiolitis, candidiasis, infectious croup, tonsillitis, varicella†, viral gastroenteritis

#### *Blood and lymphatic disorders*

*Rare:* lymphadenopathy

#### *Immune system disorders*

*Rare:* allergy/hypersensitivity





*Metabolism and nutrition disorders*

*Uncommon:* anorexia, decreased appetite

*Psychiatric disorders*

*Common:* irritability

*Uncommon:* crying, insomnia, sleep disorder

*Rare:* agitation, clinging, emotional changes

*Nervous system disorders*

*Uncommon:* febrile seizure, somnolence

*Rare:* ataxia, headache, lethargy

*Eye disorders*

*Rare:* conjunctivitis, tearing, visual discomfort

*Ear and labyrinth disorders*

*Rare:* ear pain

*Vascular disorders*

*Rare:* flushing

*Respiratory, thoracic, and mediastinal disorders*

*Uncommon:* cough, nasal congestion, respiratory congestion, rhinorrhea

*Rare:* wheezing

*Gastrointestinal disorders*

*Common:* diarrhea, vomiting

*Rare:* flatulence, nausea, teething

*Skin and subcutaneous tissue disorders*

*Common:* measles-like rash<sup>†</sup>, rash, varicella-like rash<sup>†</sup>



*Uncommon:* dermatitis (including contact, atopic, and diaper rash), eczema, erythema, miliaria rubra/heat rash, rubella-like rash<sup>†</sup>, urticaria, viral exanthema

*Rare:* acne, drug eruption, exanthema

*General disorders and administration site conditions*

*Very common:* fever  $\geq 38.9^{\circ}\text{C}$  ( $\geq 102^{\circ}\text{F}$ ) oral equivalent or abnormal<sup>†</sup>, erythema<sup>†</sup> or pain/tenderness/soreness<sup>†</sup> at the injection site

*Common:* ecchymosis or swelling<sup>†</sup> at the injection site, injection site rash<sup>†</sup>

*Uncommon:* asthenia/fatigue, induration or warmth at the injection site, injection site hemorrhage, injection site mass/lump, malaise

*Rare:* flu-like/influenza-like illness, injection site discoloration, injection site reaction, pain, pain/tenderness/soreness

*Injury and poisoning, and procedural complications*

*Rare:* contusion, non-venomous bite/sting

*Other Adverse Experiences*

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

*Infections and infestations*

atypical measles, cellulitis, epididymitis, herpes zoster, infection, influenza, measles, orchitis, parotitis, respiratory infection, skin infection, varicella (vaccine strain)

*Blood and the lymphatic system disorders*

aplastic anemia, lymphadenitis, regional lymphadenopathy, thrombocytopenia

*Immune system disorders*

anaphylactoid reaction, anaphylaxis and related phenomenon such as angioneurotic edema, facial edema, and peripheral edema, anaphylaxis in individuals with or without an allergic history

*Psychiatric disorders*



apathy, nervousness

*Nervous system disorders*

acute disseminated encephalomyelitis (ADEM), 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, 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, necrotizing retinitis (reported only in immunocompromised individuals), optic neuritis, retinitis, retrobulbar neuritis

*Ear and labyrinth disorders*

nerve deafness

*Vascular disorders*

extravasation

*Respiratory, thoracic and mediastinal disorders*

bronchial spasm, bronchitis, epistaxis, pneumonitis (see **CONTRAINDICATIONS**), pneumonia, pulmonary congestion, rhinitis, sinusitis, sneezing, sore throat

*Gastrointestinal disorders*

abdominal pain, hematochezia, mouth ulcer



*Skin and subcutaneous tissue disorders*

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

*Musculoskeletal, connective tissue and bone disorders*



arthritis and/or arthralgia (usually transient and rarely chronic [see below]), musculoskeletal pain, myalgia, pain of the hip, leg, or neck, swelling

*General disorders and administration site conditions*

injection site complaints (burning and/or stinging of short duration, eczema, edema/swelling, hive-like rash, 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

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals (see **CONTRAINDICATIONS**). No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of the combination of measles, mumps, and rubella vaccine contained in M-M-R II. Since 1978, post-marketing surveillance of M-M-R II indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (1 per 1000 reported cases).

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

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and gender, being greatest in adult females and least in prepubertal children. Following vaccination in children, reactions in joints are generally uncommon (0 to 3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (12 to 20%),

and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and adult women. Even in older women (35 to 45 years), these reactions are generally well tolerated and rarely interfere with normal activities.

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

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated measles vaccine distribution in the United States (US), the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6 to 22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the US Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

Cases of aseptic meningitis have been reported following measles, mumps, and rubella vaccination. Although a causal relationship between other strains of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

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

Safety was evaluated in an observational study that included 69,237 children vaccinated with ProQuad 12 months to 12 years old. A historical comparison group included 69,237 age-, gender-, and date-of-vaccination (day and month)-matched subjects who were given M-M-R II and VARIVAX concomitantly. The primary objective was to assess the incidence of febrile seizures occurring within various time intervals after vaccination in 12- to 60-month-old children who had neither been vaccinated against measles, mumps, rubella, or varicella, nor had a





history of the wild-type infections (N=31,298 vaccinated with ProQuad, including 31,043 who were 12 to 23 months old). The incidence of febrile seizures was also assessed in a historical control group of children who had received their first vaccination with M-M-R II and VARIVAX concomitantly (N=31,298, including 31,019 who were 12 to 23 months old). The secondary objective was to assess the general safety of ProQuad in the 30-day period after vaccination in children 12 months to 12 years old.

In pre-licensure clinical studies, an increase in fever was observed 5 to 12 days after vaccination with ProQuad (dose 1) compared to M-M-R II and VARIVAX (dose 1) given concomitantly. In the post-marketing observational surveillance study, results from the primary safety analysis revealed an approximate two-fold increase in the risk of febrile seizures in the same 5 to 12 day timeframe after vaccination with ProQuad (dose 1). The incidence of febrile seizures 5 to 12 days after ProQuad (dose 1) (0.70 per 1000 children) was higher than that in children receiving M-M-R II and VARIVAX concomitantly (0.32 per 1000 children) [relative risk (RR) 2.20, 95% confidence interval (CI): 1.04, 4.65]. The incidence of febrile seizures 0 to 30 days after ProQuad (dose 1) (1.41 per 1000 children) was similar to that observed in children receiving M-M-R II and VARIVAX concomitantly [RR 1.10 (95% CI: 0.72, 1.69)]. See Table 1. 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 1**

**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)
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In this observational post-marketing study, no case of febrile seizure was observed during the 5 to 12 day post-vaccination time period among 26,455 children who received ProQuad as a second dose of M-M-R II and/or VARIVAX (25,212 as second dose of M-M-R II and VARIVAX, 1,056 as a second dose of M-M-R II, and 187 as a second dose of VARIVAX). In addition, detailed general safety data were available from the 25,212 children who received ProQuad as a second dose of M-M-R II and VARIVAX, most of them (95%) between 4 and 6 years of age, and an analysis of these data by an independent, external safety monitoring committee did not identify any specific safety concern.

## 11. OVERDOSAGE

There are no data with regard to overdose.





## 12. CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Viral Vaccine

ATC code: J07BD54

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 syndrome.

### *Efficacy*

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

Efficacy of the measles, mumps, and rubella components of ProQuad was previously established in a series of double-blind controlled field trials with the monovalent vaccines produced by Merck, which demonstrated a high degree of protective efficacy. In these studies seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases. ProQuad elicits rates of antibody responses against measles, mumps, and rubella similar to those observed after vaccination with M-M-R II.

In combined clinical trials of VARIVAX, the protective efficacy of the vaccine against all forms of varicella ranged from 81 to 100%. In a large case-control study, the vaccine was estimated to be 85% effective against all forms of varicella and 97% effective against moderately severe and severe disease. Long-term estimated efficacy for the vaccine against all forms of varicella over 10 years was 94%. Antibody responses against varicella virus  $\geq 5$  units/mL in the glycoprotein enzyme-linked immunosorbent assay (gpELISA, a highly sensitive assay which is not commercially available) have been shown to be highly correlated with long-term protection.

Clinical studies have shown that vaccination with ProQuad elicits rates of antibody responses against varicella virus  $\geq 5$  units/mL in the gpELISA similar to those observed after vaccination with VARIVAX.

#### *Immunogenicity*

Immunogenicity was studied in children 12 through 23 months of age with a negative clinical history of measles, mumps, rubella, and varicella who participated in 5 randomized clinical trials. The immunogenicity of the current refrigerator-stable formulation was shown to be similar to the immunogenicity of the earlier formulation of ProQuad. Clinical trials also established that the earlier formulation of ProQuad is similar to the individual component vaccines (M-M-R II and VARIVAX), which are currently used in routine vaccination in some countries.

Clinical trials involving 6987 subjects who received ProQuad demonstrated detectable immune responses to measles, mumps, rubella, and varicella in a high proportion of individuals. 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. Following a single dose of ProQuad, the vaccine response rates were 97.7% for measles, 96.3 to 98.8% for mumps, and 98.8% for rubella. The vaccine response rate was 90.9% for varicella based on an antibody response rate  $\geq 5$  gpELISA units/mL (a response rate that has been shown to be highly correlated with long-term protection). These results were similar to the immune response rates induced by concomitant administration of M-M-R II and VARIVAX at separate injection sites.

#### *Persistence of Immune Response*

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2108 subjects who were involved in 1 clinical trial. The antibody persistence rates 1 year postvaccination in recipients of a single dose of ProQuad were 98.9% (1722/1741) for measles, 96.7% (1676/1733) for mumps, 99.6% (1796/1804) for rubella, and 97.5% (1512/1550) for varicella ( $\geq 5$  gpELISA units/mL).

Experience with M-M-R II demonstrates that antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination. In clinical studies



involving healthy subjects who received 1 dose of VARIVAX, detectable varicella antibodies were present in most individuals tested for up to 10 years postvaccination.

#### *Herpes Zoster*

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

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

#### *Post-Exposure Prophylaxis*

The safety and efficacy of ProQuad for use after exposure to measles, mumps, rubella, or varicella have not been established. No clinical data are available for ProQuad administered after exposure to measles, mumps, rubella, or varicella.

#### *Reye Syndrome*

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

#### *Studies with Other Vaccines*

In a clinical trial involving 1913 healthy subjects 12 through 15 months of age, 949 received ProQuad, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP)



and *Haemophilus b* Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine concomitantly at separate injection sites. Another 485 healthy subjects received ProQuad at the initial visit followed by DTaP and *Haemophilus b* Conjugate and Hepatitis B (Recombinant) Vaccine given concomitantly 6 weeks later. In subjects 13.5 months of age or older, seroconversion rates and antibody titers were comparable between the 2 groups at approximately 6 weeks postvaccination. However, in subjects less than 13.5 months of age, seroconversion rates and antibody titers were comparable between the 2 groups for each of the vaccine components except pertussis FHA (see **DRUG INTERACTIONS**). No clinically significant differences in adverse experiences were reported between the 2 treatment groups.

In a clinical trial involving 1027 healthy children 12 to 15 months of age, 510 were randomized to receive ProQuad and Prevnar concomitantly at separate injection sites, and 517 were randomized to receive ProQuad and Prevnar non-concomitantly. Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, and *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were comparable in the concomitant and non-concomitant groups at 6 weeks post-vaccination indicating that ProQuad and Prevnar can be administered concomitantly at separate injection sites. No clinically significant differences in adverse events were reported between treatment groups.

In a clinical trial involving 1800 healthy children 12 to 23 months of age, 1453 were randomized to receive 2 doses of VAQTA, and 347 were randomized to receive 2 doses of VAQTA concomitantly with 2 doses ProQuad at least 6 months apart. Rates of adverse experiences were lower following a second dose than following the first dose of both vaccines given concomitantly.

In a clinical trial involving 653 healthy children 12 to 15 months of age, 330 were randomized to receive VAQTA, ProQuad, and Prevnar concomitantly, and 323 were randomized to receive ProQuad and Prevnar concomitantly followed by VAQTA 6 weeks later. Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, and *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were comparable between the 3 groups at 6 weeks post-vaccination indicating that ProQuad, VAQTA, and Prevnar can be administered concomitantly at separate

injection sites. No clinically significant differences in adverse events were reported among treatment groups.

In the above 3 post-licensure clinical trials evaluating the concomitant use of ProQuad with other pediatric vaccines, a total of 1745 children 12 to 23 months of age received 2 doses of ProQuad, of which 1661 completed safety follow-up after both doses. Rates of adverse experiences after the second dose of ProQuad were generally similar to, or lower than, those seen with the first dose. The fever rate was lower after the second dose than after the first dose.

### 13. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data to suggest that ProQuad affects the ability to drive or operate machinery.

### 14. ANIMAL TOXICOLOGY

#### *Carcinogenesis, Mutagenesis, Reproduction*

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

List of excipients:  $\frac{p}{f}$   $\frac{29}{4}$  '19.

Sucrose, gelatin, sodium chloride, sorbitol, monosodium L-glutamated  
monohydrate, sodium phosphate, sodium bicarbonate, potassium  
phosphate, potassium chloride, ~~stabilizer~~ urea.



## 15. 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, but not exceed temperatures lower than 50°C ( 58°F). Use of dry ice may subject ProQuad to temperatures colder than 50°C ( 58°F).

Before reconstitution, store the lyophilized vaccine in a refrigerator at 2° to 8°C (36° to 46°F) or colder. The 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 IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.**

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

MENGANDUNG BABI

**HARUS DENGAN RESEP DOKTER**

Shelf life: 18 months

**Registration No.**

Box, 1 vial @ 0,5 mL + 1 vial of diluent – Reg No. DKIXXXXXXXXXX

Manufactured by:





Merck Sharp & Dohme Corp.,  
West Point, PA. 19486, U.S.A

Packaged & released by:  
Merck Sharp Dohme B.V  
Haarlem. Netherlands

Registered by:  
PT. Merck Sharp Dohme Pharma Tbk  
Pasuruan, Jawa Timur

PI Version 1.1  
S-LPC-V221-I-ref-092016

