

**M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live)
Suspension for subcutaneous injection**

الادارة المركزية للمعاير والجودة
والدواء والمستحضرات الجوية والمتكررة
ادارة تسجيل المستحضرات الجوية
نشرة مقتددة ... ٢٠١٤ : ٣٢٦٧ رقم
التاريخ ٢٠١٤-٠٩-٢٠١٥

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

M-M-R® II is a vaccine indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

2 DOSAGE AND ADMINISTRATION

For subcutaneous use only.

2.1 Dose and Schedule

Each 0.5 mL dose is administered subcutaneously.

The first dose is administered at 12 to 15 months of age. A second dose is administered at 4 to 6 years of age.

The second dose may be administered prior to 4 years of age, provided that there is a minimum interval of one month between the doses of measles, mumps and rubella virus vaccine, live.

Children who received an initial dose of measles, mumps and rubella vaccine prior to their first birthday should receive additional doses of vaccine at 12-15 months of age and at 4-6 years of age to complete the vaccination series [see *Clinical Studies* (14.2)].

For post-exposure prophylaxis for measles, administer a dose of M-M-R II vaccine within 72 hours after exposure.

2.2 Preparation and Administration

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

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

Withdraw the entire volume of the reconstituted vaccine and inject subcutaneously into the outer aspect of the upper arm (deltoid region) or into the higher anterolateral area of the thigh.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Visually inspect the vaccine before and after reconstitution prior to administration. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug, when reconstituted, is a clear yellow liquid. Discard if particulate matter or discoloration are observed in the reconstituted vaccine.

To minimize loss of potency, administer M-M-R II as soon as possible after reconstitution. If not used immediately, the reconstituted vaccine may be stored between 2°C to 8°C, protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer M-M-R II vaccine to individuals with a history of hypersensitivity to any component of the vaccine (including gelatin) or who have experienced a hypersensitivity reaction following administration of a previous dose of M-M-R II vaccine or any other measles, mumps and rubella-containing vaccine. Do not administer M-M-R II vaccine to individuals with a history of anaphylaxis to neomycin [see Description (11)].

4.2 Immunosuppression

Do not administer M-M-R II vaccine to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy. Measles inclusion body encephalitis (MIBE), pneumonitis and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

Do not administer M-M-R II to individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

4.3 Moderate or Severe Febrile Illness

Do not administer M-M-R II vaccine to individuals with an active febrile illness with fever >38.5°C.

4.4 Active Untreated Tuberculosis

Do not administer M-M-R II vaccine to individuals with active untreated tuberculosis (TB).

4.5 Pregnancy

Do not administer M-M-R II to individuals who are pregnant or who are planning on becoming pregnant within the next month [see *Use in Specific Populations (8.1)* and *Patient Counseling Information (17)*].

5 WARNINGS AND PRECAUTIONS

5.1 Febrile Seizure

There is a risk of fever and associated febrile seizure in the first 2 weeks following immunization with M-M-R II vaccine. For children who have experienced a previous febrile seizure (from any cause) and those with a family history of febrile seizures there is a small increase in risk of febrile seizure following receipt of M-M-R II vaccine [see *Adverse Reactions (6)*].

5.2 Hypersensitivity to Eggs

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

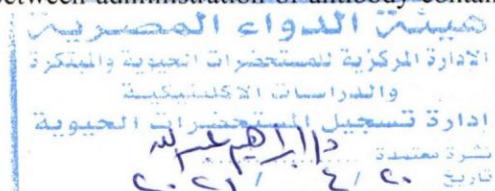
5.3 Thrombocytopenia

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

5.4 Immune Globulins and Transfusions

Immune Globulins (IG) and other blood products should not be given concurrently with M-M-R II [see *Drug Interactions* (7.2)]. These products may contain antibodies that interfere with vaccine virus replication and decrease the expected immune response.

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



6 ADVERSE REACTIONS

The following adverse reactions include those identified during clinical trials or reported during post-approval use of M-M-R II vaccine or its individual components.

APPENDIX B

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis

Digestive System

Pancreatitis: diarrhea: vomiting: parotitis: nausea

Hematologic and Lymphatic Systems

Thrombocytopenia; purpura; regional lymphadenopathy; leukocytosis

The Immune System

Anaphylaxis, anaphylactoid reactions, angioedema (including peripheral or facial edema) and bronchial spasm.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

polyneuropathy, 35 Respiratory System

Pneumonia; pneumonitis; sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; acute hemorrhagic edema of infancy; Henoch-Schönlein purpura; erythema multiforme; urticaria; rash; measles-like rash; pruritus; injection site reactions (pain, erythema, swelling and vesiculation).

Special Senses — Ear

Nerve deafness: otitis media

Nerve deafness, &c. Special Senses — Eye

Retinitis; optic neuritis; papillitis; conjunctivitis.

Retinitis, optic Urogenital System

Epididymitis; orchitis

7 DEBUG INTERACTIONS

7.1 Corticosteroids and Immunosuppressive Drugs

M-M-R II vaccine should not be administered to individuals receiving immunosuppressive therapy, including high dose corticosteroids. Vaccination with M-M-R II vaccine can result in disseminated disease due to measles vaccine in individuals on immunosuppressive drugs [see *Contraindications* (4.2)].

7.2 Immune Globulins and Transfusions

Administration of immune globulins and other blood products concurrently with M-M-R II vaccine may interfere with the expected immune response [see *Warnings and Precautions (5.4)*]. The ACIP has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

7.3 Tuberculin Skin Testing

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 skin test with tuberculin purified protein derivative (PPD) is to be done, it should be administered before, simultaneously with, or at least 4 to 6 weeks after vaccination with M-M-R II vaccine.

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 تاريخ ٢٠١٤

7.4 Use with Other Live Viral Vaccines

M-M-R II vaccine can be administered concurrently with other live viral vaccines. If not given concurrently, M-M-R II vaccine should be given one month before or one month after administration of other live viral vaccines to avoid potential for immune interference.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

M-M-R II vaccine is contraindicated for use in pregnant women because infection during pregnancy with the wild-type viruses has been associated with maternal and fetal adverse outcomes.

Increased rates of spontaneous abortion, stillbirth, premature delivery and congenital defects have been observed following infection with wild-type measles during pregnancy. Wild-type mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion.

Infection with wild-type rubella during pregnancy can lead to miscarriage or stillbirth. If rubella infection occurs during the first trimester of pregnancy, it can result in severe congenital defects, Congenital Rubella Syndrome (CRS). Congenital rubella syndrome in the infant includes but is not limited to eye manifestations (cataracts, glaucoma, retinitis), congenital heart defects, hearing loss, microcephaly, and intellectual disabilities. M-M-R II vaccine contains live attenuated measles, mumps and rubella viruses. It is not known whether M-M-R II vaccine can cause fetal harm when administered to pregnant woman. There are no adequate and well-controlled studies of M-M-R II vaccine administration to pregnant women.

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

Available data suggest the rates of major birth defects and miscarriage in women who received M-M-R II vaccine within 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates (*see Data*).

Data

Human Data

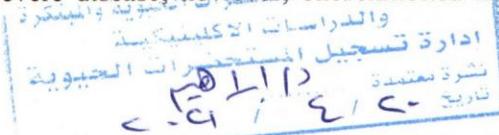
A cumulative assessment of post-marketing reports for M-M-R II vaccine from licensure 01 April 1978 through 31 December 2018, identified 796 reports of inadvertent administration of M-M-R II vaccine occurring 30 days before or at any time during pregnancy with known pregnancy outcomes. Of the prospectively followed pregnancies for whom the timing of M-M-R II vaccination was known, 425 women received M-M-R II vaccine during the 30 days prior to conception through the second trimester. The outcomes for these 425 prospectively followed pregnancies included 16 infants with major birth defects, 4 cases of fetal death and 50 cases of miscarriage. No abnormalities compatible with congenital rubella syndrome have been identified in patients who received M-M-R II vaccine. Rubella vaccine viruses can cross the placenta, leading to asymptomatic infection of the fetus. Mumps vaccine virus has also been shown to infect the placenta, but there is no evidence that it causes congenital malformations or disease in the fetus or infant.

The CDC established the Vaccine in Pregnancy registry (1971-1989) of women who had received rubella vaccines within 3 months before or after conception. Data on 1221 inadvertently vaccinated pregnant women demonstrated no evidence of an increase in fetal abnormalities or cases of Congenital Rubella Syndrome (CRS) in the enrolled women .

8.2 Lactation

Risk Summary

It is not known whether measles or mumps vaccine 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 breast-fed infants with serological evidence of rubella virus vaccine strain antibodies, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella.



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

8.4 Pediatric Use

M-M-R II vaccine is not approved for individuals less than 12 months of age. Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established [see *Clinical Studies (14)*]. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

8.5 Geriatric Use

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 Description

M-M-R II vaccine is a sterile lyophilized preparation of (1) Measles Virus Vaccine Live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts. The cells, virus pools, recombinant human serum albumin and fetal bovine serum used in manufacturing are tested and determined to be free of adventitious agents.

After reconstitution, each 0.5 mL dose contains not less than $3.0 \log_{10}$ TCID₅₀ (tissue culture infectious doses) of measles virus; $4.1 \log_{10}$ TCID₅₀ of mumps virus; and $3.0 \log_{10}$ TCID₅₀ of rubella virus.

Each dose is calculated to contain sorbitol (14.5 mg), sucrose (1.9 mg), hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤ 0.3 mg), fetal bovine serum (<1 ppm), and approximately 25 mcg of neomycin. The product contains no preservative.

Each dose also contains Medium 199 with Hank's Salts, Minimum Essential Medium Eagle, monosodium L-glutamate monohydrate, phenol red, potassium phosphate dibasic, potassium phosphate monobasic, sodium bicarbonate, sodium phosphate dibasic, and sodium phosphate monobasic.

Sodium

This medicinal product contains less than 1 mmol sodium (23 milligrams) per dose, that is to say essentially 'sodium-free'.

Potassium

This medicinal product contains less than 1 mmol potassium (39 milligrams) per dose, that is to say essentially 'potassium-free'.

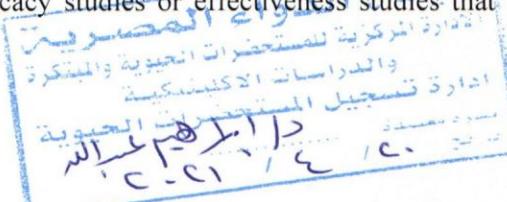
Sorbitol (E 420)

This medicinal product contains 14.5 milligrams of sorbitol per dose. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

12 clinical pharmacology

12.1 Mechanism of Action

M-M-R II vaccination induces antibodies to measles, mumps, and rubella associated with protection which can be measured by neutralization assays, hemagglutination-inhibition (HI) assays, or enzyme linked immunosorbent assay (ELISA) tests. Results from efficacy studies or effectiveness studies that



were previously conducted for the component vaccines of M-M-R II were used to define levels of serum antibodies that correlated with protection against measles, mumps, and rubella [see Clinical Studies (14)].

12.6 Persistence of Antibody Responses After Vaccination

Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in 95-100%, 74-91%, and 90-100% of individuals respectively, 11 to 13 years after primary vaccination.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

14.1 Clinical Efficacy

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled trials. These studies also established that seroconversion in response to vaccination against measles, mumps and rubella paralleled protection.

14.2 Immunogenicity

Clinical studies enrolling 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II vaccine is immunogenic. In these studies, a single injection of the vaccine induced measles HI antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible individuals.

A study of 6-month-old and 15-month-old infants born to mothers vaccinated with a measles vaccine in childhood, demonstrated that, following infant and toddler vaccination with Measles Virus Vaccine, Live (previously US-licensed, manufactured by Merck), 74% of the 6-month-old infants developed detectable neutralizing antibody titers while 100% of the 15-month-old infants vaccinated with Measles Virus Vaccine, Live or M-M-R II vaccine developed neutralizing antibodies . When the 6-month-old infants of immunized mothers were revaccinated at 15 months with M-M-R II vaccine, they developed antibody titers similar to those of toddlers who were vaccinated previously at 15-months of age.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4681 -M-M-R II vaccine is supplied as follows:

- (1) a box of 10 single-dose vials of lyophilized vaccine (package A)
 - (2) a box of one single-dose vial of lyophilized vaccine
 - (3) a box of 10 vials of diluent (package B)
 - (4) a box of single-dose vial of lyophilized vaccine and 1 vial of sterile diluent.
- Not all pack sizes may be marketed.

Exposure to light may inactivate the vaccine viruses.

Before reconstitution, refrigerate the lyophilized vaccine at 2°C to 8°C.

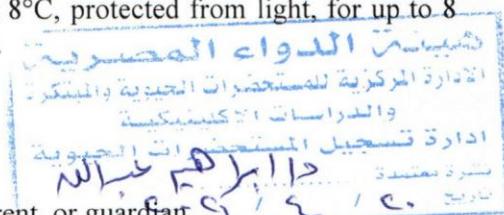
Store accompanying diluent in the refrigerator with the lyophilized vaccine or separately at room temperature below 30°C. **Do not freeze the diluent.**

Administer M-M-R II vaccine as soon as possible after reconstitution. If not administered immediately, reconstituted vaccine may be stored between 2°C to 8°C, protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

17 PATIENT COUNSELING INFORMATION

Discuss the following with the patient:

- Provide the required vaccine information to the patient, parent, or guardian.
- Inform the patient, parent, or guardian of the benefits and risks associated with vaccination.



- Question the patient, parent, or guardian about reactions to a previous dose of M-M-R II vaccine or other measles-, mumps-, or rubella-containing vaccines.
- Question females of reproductive potential regarding the possibility of pregnancy. Inform female patients to avoid pregnancy for 1 month following vaccination [see *Contraindications (4.5) and Use in Specific Populations (8.1)*].
- Inform the patient, parent, or guardian that vaccination with M-M-R II may not offer 100% protection from measles, mumps, and rubella infection.
- Instruct patients, parents, or guardians to report any adverse reactions to their health-care provider.

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Released by:

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For patent information: www.merck.com/product/patent/home.html

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(THIS IS A MEDICAMENT)

-Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

-Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.

-The doctor and the pharmacist are experts in medicine, its benefits and risks.

-Do not by yourself interrupt the period of treatment prescribed for you.

-Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

