M-M-R® II
(MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

1. NAME OF THE MEDICINAL PRODUCT

M-M-R II powder and solvent for suspension for injection
Measles, mumps, and rubella vaccine (live)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 ml) contains:

Measles virus[1] Enders' Edmonston strain (live, attenuated) ……..….not less than $1x10^3$ $CCID_{50}$*
Mumps virus[1] Jeryl Lynn™ [Level B] strain (live, attenuated)……..…not less than $12.5x10^3$ $CCID_{50}$*
Rubella virus[2] Wistar RA 27/3 strain (live, attenuated) ……..….not less than $1x10^3$ $CCID_{50}$*

*50% cell culture infectious dose

[1] produced in chick embryo cells.
[2] produced in WI-38 human diploid lung fibroblasts.

The vaccine may contain traces of recombinant human albumin (rHA).
This vaccine contains a trace amount of neomycin. See section 4.3.

Excipients with known effect:
The vaccine contains 14.5 mg of sorbitol. See section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.
Before reconstitution, the powder is a light yellow compact crystalline cake and the solvent is a clear colourless fluid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals from 12 months of age (see section 4.2).

M-M-R II can be administered to infants from 9 months of age under special circumstances (see sections 4.2, 4.4 and 5.1).

For use in measles outbreaks, or for post-exposure vaccination, or, for use in previously unvaccinated individuals older than 9 months who are in contact with susceptible pregnant women, and persons likely to be susceptible to mumps and rubella, see section 5.1.

M-M-R II is to be used on the basis of official recommendations.

4.2 Posology and method of administration

Posology

Individuals 12 months of age or older:
Individuals 12 months or older should receive one dose at an elected date. A second dose may be administered at least 4 weeks after the first dose in accordance with official recommendation. The second dose is intended for individuals who did not respond to the first dose for any reason.

Infants between 9 and 12 months of age:
Immunogenicity and safety data show that M-M-R II can be administered to infants between 9 and 12 months of age, in accordance with official recommendations or when an early protection is considered necessary (e.g., day-care, outbreak situations, or travel to a region with high prevalence of measles). Such infants should be revaccinated at 12 to 15 months of age. An additional dose with a measles-containing vaccine should be considered according to official recommendations (see sections 4.4 and 5.1).

Infants below 9 months of age:
No data on the efficacy and safety of M-M-R II for use in children below 9 months of age are currently available.

Method of administration

The vaccine is to be injected intramuscularly (IM) or subcutaneously (SC).

The preferred injection sites are the anterolateral area of the thigh in younger children and the deltoid area in older children, adolescents, and adults.
The vaccine should be administered subcutaneously in patients with thrombocytopenia or any coagulation disorder.

For precautions to be taken before handling or administering the medicinal product, and for instructions on reconstitution of the medicinal product before administration, see section 6.6.

DO NOT INJECT INTRAVASCULARLY.

4.3 Contraindications

History of hypersensitivity to any measles, mumps, or rubella vaccine, or to any of the excipients, including neomycin (see sections 2, 4.4, and 6.1).

Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

Vaccination should be postponed during any illness with fever >38.5°C.

Active untreated tuberculosis. Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine. No studies have been reported to date on the effect of measles virus vaccines on children with untreated tuberculosis.

Blood dyscrasias, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the haematopoietic and lymphatic systems.

Current immunosuppressive therapy (including high doses of corticosteroids). M-M-R II is not contraindicated in individuals who are receiving topical or low-dose parenteral corticosteroids (*e.g.* for asthma prophylaxis or replacement therapy).

Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinemia and AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25% %; children between 12-35 months: CD4+ < 20%; children between 36-59 months: CD4+ < 15% (see section 4.4).

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.

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

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine (see section 4.8).

Adults and adolescents with a history of allergies may potentially be at increased risk of anaphylaxis or anaphylactoid reactions. Close monitoring is recommended following vaccination for the early signs of such reactions.

Since 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. The potential risk-to-benefit ratio should be carefully evaluated before considering vaccination in such cases.

Due caution should be employed in administration of M-M-R II to persons with individual or family history of convulsions, or a history of cerebral injury. The physician should be alert to the temperature elevation that may occur following vaccination (see section 4.8).

Infants from 9 to 12 months of age vaccinated with a measles-containing vaccine during measles outbreaks or for other reasons may fail to respond to the vaccine due to the presence of circulating antibodies of maternal origin and/or immaturity of the immune system (see sections 4.2 and 5.1).

This vaccine contains 14.5 mg of sorbitol as an excipient. Patients with rare hereditary problems of fructose intolerance should not take this vaccine.

Thrombocytopenia

This vaccine should be given subcutaneously to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals. Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) 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 in such cases (see section 4.8).

Other

Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (asymptomatic HIV patients, IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases).

Immunocompromised patients who have no contraindication for this vaccination (see section 4.3) may not respond as well as immunocompetent patients; therefore, some of these patients may acquire measles, mumps, or rubella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of measles, parotitis, and rubella.

Vaccination with M-M-R II may not result in protection in all vaccinees.

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 without any evidence of clinical disease (see section 4.6).

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 vaccinees to susceptible contacts.

Interference with laboratory tests: see section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

Immune globulin
Immune globulin (IG) is not to be given concomitantly with M-M-R II.

Administration of immune globulins concomitantly with M-M-R II may interfere with the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of human immune serum globulin.

Administration of measles, mumps, or rubella antibody-containing blood products, including immune globulin preparations, should be avoided within 1 month after a dose of M-M-R II unless considered to be essential.

Laboratory tests
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 4 to 6 weeks after vaccination with M-M-R II.

Use with other vaccines
Currently no specific studies have been conducted on the concomitant use of M-M-R II and other vaccines. However, since M-M-R II has been shown to have safety and immunogenicity profiles similar to the previous formulation of the combined measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., experience with this vaccine can be considered.

Published clinical data support concomitant administration of the previous formulation of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. with other childhood vaccinations, including DTaP (or DTwP), IPV (or OPV), HIB (*Haemophilus influenzae* type b), HIB-HBV (*Haemophilus influenzae* type b with Hepatitis B vaccine), and VAR (varicella). M-M-R II should be given concomitantly at separate injection sites, or one month before or after administration of other live virus vaccines.

Based on clinical studies with the quadrivalent measles, mumps, rubella and varicella vaccine and with the previous formulation of the combined measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc., M-M-R II can be given simultaneously (but at separate injection sites) with Prevenar and/or hepatitis A vaccine. In these clinical studies, it was demonstrated that the immune responses were unaffected and that the overall safety profiles of the administered vaccines were similar.

4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnant women should not be vaccinated with M-M-R II.

Studies have not been conducted with M-M-R II in pregnant women. It is not known whether M-M-R II can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity.

However, foetal damage has not been documented when measles or mumps vaccines have been given to pregnant women. Although a theoretical risk cannot be excluded, no cases of congenital rubella syndrome have been reported in more than 3500 susceptible women who were unknowingly in early stages of pregnancy when vaccinated with a rubella-containing vaccine. Therefore, inadvertent vaccination of unknowingly pregnant women with measles-, mumps-, or rubella-containing vaccines should not be a reason for termination of pregnancy.

Pregnancy should be avoided for 1 month following vaccination. Women who intend to become pregnant should be advised to delay.

Breast-feeding
Studies have shown that breast-feeding postpartum women vaccinated with live attenuated rubella vaccines may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection, none had symptomatic disease. It is not known whether measles or mumps vaccine virus is secreted in human milk; therefore, caution should be exercised when M-M-R II is administered to a breast-feeding woman.

Fertility
M-M-R II has not been evaluated in fertility studies.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. M-M-R II is expected to have no or negligible influence on ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile
In clinical trials, M-M-R II was administered to 1965 children (see section 5.1), and the general safety profile was comparable to the previous formulation of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.

In a clinical trial, 752 children received M-M-R II, either intramuscularly or subcutaneously. The general safety profile of either administration routes were comparable, although injection-site reactions were less frequent in the IM group (15.8%) compared with the SC group (25.8%).

All adverse reactions were evaluated in 1940 children. Among these children, the vaccine-related adverse reactions, summarised in section b, were observed in individuals following vaccination with M-M-R II (excluding isolated reports with frequency <0.2%).

In comparison to the first dose, a second dose of M-M-R II is not associated with an increase in the incidence and severity of clinical symptoms including those suggestive of hypersensitivity reaction.

Additionally, other adverse reactions reported with post-marketing use of M-M-R II and/or in clinical studies and post-marketing use of previous formulations of monovalent and of the combined measles, mumps, and rubella vaccines manufactured by Merck & Co., Inc. without regard to causality or frequency are available and are summarised in section b. The frequency of these adverse events is

qualified as "not known" when it cannot be estimated based on the available data. These data were reported based on more than 400 million doses distributed worldwide.

The most common adverse reactions reported with the use of M-M-R II were: fever (38.5°C or higher); injection site reactions including pain, swelling and erythema.

b. Tabulated list of adverse reactions

Adverse reactions are ranked under headings of frequency using the following convention: [Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to ≤1/100); Not known (cannot be estimated from the available data)]

Adverse reactions	Frequency
Infections and infestations	
Nasopharyngitis, Upper respiratory tract infection or Viral infection	Uncommon
Aseptic meningitis†, Atypical measles, Epididymitis, Orchitis, Otitis media, Parotitis, Rhinitis, Subacute Sclerosing Panencephalitis†	Not known
Blood and the lymphatic system disorders	
Regional lymphadenopathy, Thrombocytopenia	Not known
Immune system disorders	
Anaphylactoid reaction, Anaphylaxis and related phenomenon such as Angioneurotic oedema, Facial oedema, and Peripheral oedema	Not known
Psychiatric disorders	
Crying	Uncommon
Irritability	Not known
Nervous system disorders	
Afebrile convulsions or seizures, Ataxia, Dizziness, Encephalitis†, Encephalopathy†, Febrile convulsion (in children), Guillain-Barre syndrome, Headache, Measles inclusion body encephalitis (MIBE) (see section 4.3), Ocular palsies, Optic neuritis, Paraesthesia, Polyneuritis, Polyneuropathy, Retrobulbar neuritis, Syncope	Not known
Eye disorders	
Conjunctivitis, Retinitis	Not known
Ear and labyrinth disorders	
Nerve deafness	Not known
Respiratory, thoracic, and mediastinal disorders	
Rhinorrhoea	Uncommon
Bronchial spasm, Cough, Pneumonia, Pneumonitis (see section 4.3), Sore throat	Not known
Gastrointestinal disorders	
Diarrhoea or Vomiting	Uncommon
Nausea	Not known
Skin and subcutaneous tissue disorders	
Rash morbilliform or other Rash	Common
Urticaria	Uncommon
Panniculitis, Pruritus, Purpura, Skin induration, Stevens-Johnson syndrome	Not known
Musculoskeletal, connective tissue and bone disorders	
Arthritis† and/or Arthralgia† (usually transient and rarely chronic), Myalgia	Not known
General disorders and administration site conditions	

Fever (38.5°C or higher), Injection site erythema, Injection site pain, and Injection site swelling	Very common
Injection site bruising	Common
Injection site rash	Uncommon
Burning and/or Stinging of short duration at the injection site, Malaise, Papillitis, Peripheral oedema, Swelling, Tenderness, Vesicles at the injection site, Wheal and Flare at the injection site	Not known
Vascular disorders	
Vasculitis	Not known

† see section c

c. Description of selected adverse reactions

Aseptic meningitis

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.

Encephalitis and Encephalopathy

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 section 4.3); disseminated mumps and rubella vaccine virus infection has also been reported.

Subacute sclerosing panencephalitis

There is no evidence that measles vaccine can cause SSPE. There have been reports of 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. 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 risk of SSPE.

Arthralgia and/or arthritis

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 sex, being greatest in adult females and least in prepubertal children. Following vaccination in children, reactions in joints are generally uncommon (0-3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (12-20%), 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 (35-45 years), these reactions are generally well tolerated and rarely interfere with normal activities.

Chronic arthritis

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Administration of a higher than recommended dose of M-M-R II was reported rarely and the adverse reaction profile was comparable to that observed with the recommended dose of M-M-R II.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccine, ATC code J07BD52

Evaluation of immunogenicity and clinical efficacy
A comparative study in 1279 subjects who received M-M-R II or the previous formulation (manufactured with human serum albumin) of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. demonstrated similar immunogenicity and safety between the 2 products.

Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that the previous formulation of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95%, mumps neutralising antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons.

Evaluation of immunogenicity in children from 9 to 12 months of age at the time of first dose
A clinical study was conducted with the quadrivalent measles, mumps, rubella and varicella vaccine manufactured by Merck & Co., Inc., administered with a 2-dose schedule, the doses being given 3 months apart in 1,620 healthy subjects from 9 to 12 months of age at the time of first dose. The safety profile post-dose 1 and 2 was generally comparable for all age cohorts.

In the Full Analysis Set (vaccinated subjects regardless of their antibody titre at baseline), high seroprotection rates of >99% were elicited to mumps and rubella post-dose 2, regardless of the age of the vaccinee at the first dose. After 2 doses, the seroprotection rates against measles were 98.1% when the first dose was given at 11 months compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective met). After two doses, the seroprotection rates against measles were 94.6% when the first dose was given at 9 months compared to 98.9% when the first dose was given at 12 months (non-inferiority study objective not met).

The seroprotection rates to measles, mumps, and rubella for the Full Analysis Set are given in Table 1.

Table 1: Seroprotection Rates to Measles, Mumps, and Rubella 6 Weeks Post-Dose 1 and 6 Weeks Post-Dose 2 of the quadrivalent measles, mumps, rubella and varicella vaccine manufactured by Merck & Co., Inc. – Full Analysis Set

Valence (seroprotection level)	**Time point**	**Dose 1 at 9 months / Dose 2 at 12 months N = 527**	**Dose 1 at 11 months / Dose 2 at 14 months N = 480**	**Dose 1 at 12 months / Dose 2 at 15 months N = 466**
		Seroprotection rates [95% CI]	**Seroprotection rates [95% CI]**	**Seroprotection rates [95% CI]**
Measles (titre ≥255 mIU/mL)	**Post-Dose 1**	72.3% [68.2; 76.1]	87.6% [84.2; 90.4]	90.6% [87.6; 93.1]
	Post-Dose 2	94.6% [92.3; 96.4]	98.1% [96.4; 99.1]	98.9% [97.5; 99.6]
Mumps (titre ≥10 ELISA Ab units/mL)	**Post-Dose 1**	96.4% [94.4; 97.8]	98.7% [97.3; 99.5]	98.5% [96.9; 99.4]
	Post-Dose 2	99.2% [98.0; 99.8]	99.6% [98.5; 99.9]	99.3% [98.1; 99.9]

Rubella (titre ≥10 IU/mL)	**Post-Dose 1**	97.3% [95.5; 98.5]	98.7% [97.3; 99.5]	97.8% [96.0; 98.9]
	Post-Dose 2	99.4% [98.3; 99.9]	99.4% [98.1; 99.9]	99.6% [98.4; 99.9]

The post-dose 2 geometric mean titres (GMTs) against mumps and rubella were comparable across all age categories, while the GMTs against measles were lower in subjects who received the first dose at 9 months of age as compared to subjects who received the first dose at 11 or 12 months of age.

A comparative study in 752 subjects who received M-M-R II either by intramuscular route or subcutaneous route demonstrated a similar immunogenicity profile between both administration routes.

The efficacy of the components of the previous formulation of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. was established in a series of double-blind controlled field trials, which demonstrated a high degree of protective efficacy afforded by the individual vaccine components. These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases.

Post-exposure vaccination
Vaccination of individuals exposed to wild-type measles may provide some protection if the vaccine can be administered within 72 hours after exposure. If, however, the vaccine is given a few days before exposure, substantial protection may be afforded. There is no conclusive evidence that vaccination of individuals recently exposed to wild-type mumps or wild-type rubella will provide protection.

Effectiveness
More than 400 million doses of the previous formulation of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. have been distributed worldwide (1978 to 2003). Widespread use of a 2-dose vaccination schedule in the United States and countries such as Finland and Sweden has led to a >99% reduction in the incidence of each of the 3 targeted diseases.

Non-pregnant adolescent and adult females
Vaccination of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see sections 4.4 and 4.6). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which, in turn, prevents infection of the foetus and consequent congenital rubella injury.

Previously unvaccinated individuals older than 9 months who are in contact with susceptible pregnant women should receive live attenuated rubella-containing vaccine (such as M-M-R II or a monovalent rubella vaccine) to reduce the risk of exposure of the pregnant woman.

Individuals likely to be susceptible to mumps and rubella
M-M-R II is preferred for vaccination of persons likely to be susceptible to mumps and rubella. Individuals who require vaccination against measles can receive M-M-R II regardless of their immune status to mumps or rubella if a monovalent measles vaccine is not readily available.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sorbitol
Sodium phosphate, monobasic
Sodium phosphate, dibasic
Potassium phosphate, monobasic
Potassium phosphate, dibasic
Sucrose
Hydrolysed (porcine) gelatin
Medium 199 with Hanks' salts
Minimum Essential Medium, Eagle (MEM)
Monosodium L-glutamate
Neomycin
Phenol red
Sodium bicarbonate

Solvent
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, the vaccine must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After reconstitution, the vaccine should be used immediately; however, in-use stability has been demonstrated for 8 hours when refrigerated at 2°C-8°C.

6.4 Special precautions for storage

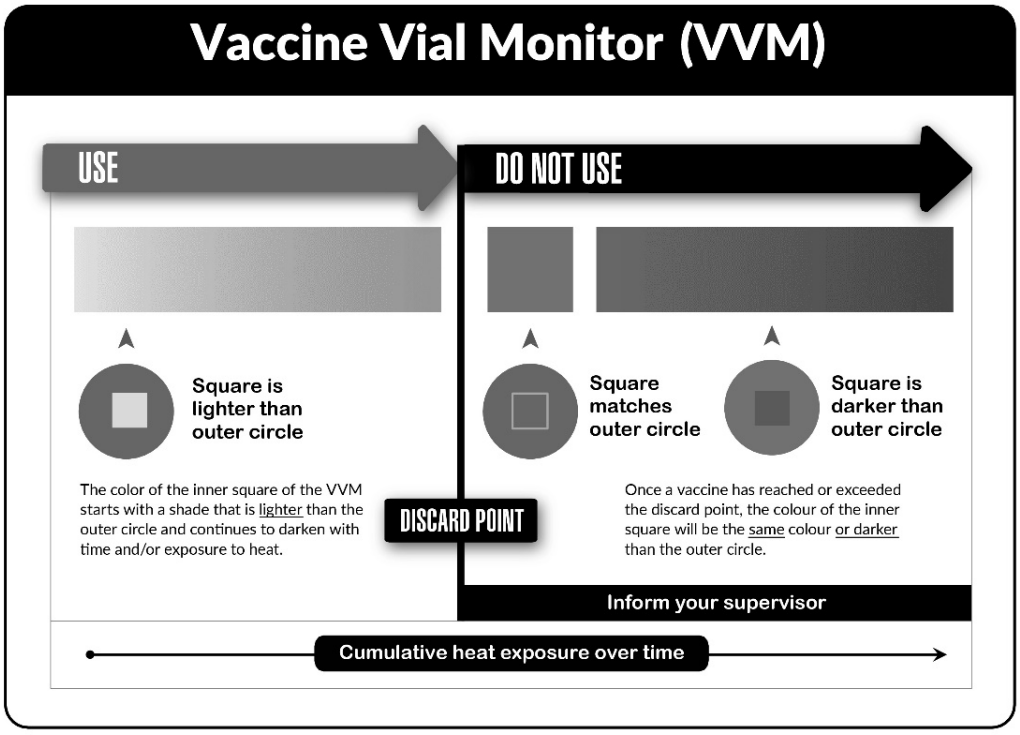
Store and transport refrigerated (2°C – 8°C).
Do not freeze.
Keep the vial of powder in the outer carton in order to protect from light.

For storage conditions after the reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

M-M-R II is supplied as a box of 10 single-dose vials of lyophilized vaccine and a box of 10 vials of diluent.

Fig. 1 The Vaccine Vial Monitor



The Vaccine Vial Monitors (VVMs) are on the cap of M-M-R II manufactured by Merck & Co., Inc. The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

6.6 Special precautions for disposal and other handling

To reconstitute, use the solvent supplied. The solvent is a clear colourless liquid. Before mixing with the solvent, the powder is a light yellow compact crystalline cake. When completely reconstituted, the vaccine is a clear yellow liquid.

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.

Reconstitution instructions
Withdraw the entire volume of solvent into a syringe to be used for reconstitution and injection. Inject the entire content of the syringe into the vial containing the powder. Gently agitate to mix thoroughly. The reconstituted vaccine must not be used if any particulate matter is noted or if the appearance of the solvent or powder or of the reconstituted vaccine differs from that described above.

Withdraw the entire content of the reconstituted vaccine vial into the same syringe and inject the entire volume.

If two needles are provided: use one needle to reconstitute the vaccine and the other for its administration to the person to be vaccinated.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.