ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

M-M-RVAXPRO
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.

For a 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-RVAXPRO is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months or older (see section 4.2).

M-M-RVAXPRO 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 than9 months who are in contact with susceptible pregnant women, and persons likely to be susceptible to mumps and rubella, see section 5.1.

4.2 Posology and method of administration

Posology

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

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-RVAXPRO 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. 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-RVAXPRO 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.

Precautions to be taken before handling or administering the medicinal product.
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 (see also sections 4.4 and 4.6).

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

Active untreated tuberculosis (see section 4.4).

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-RVAXPRO is not contraindicated in individuals who are receiving topical or low-dose parenteral corticosteroids (*e.g.* for asthma prophylaxis or replacement therapy).

Humoral or cellular (primary or acquired) immunodeficiency, including hypogammaglobulinemia and dysgammaglobulinemia and AIDS, or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage <25% (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

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

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-RVAXPRO 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).

The vaccine contains 1.9 mg of sucrose as an excipient. This amount is too low to cause adverse events in patients with rare hereditary problems such as fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.

The vaccine contains residual traces of recombinant human albumin (rHA). In a study with children receiving a second dose of M-M-RVAXPRO, sensitisation to rHA was not observed. A theoretical risk of hypersensitivity to rHA at a low frequency cannot be ruled out. Therefore caution needs to be exercised when using any product containing rHA in individuals who previously showed signs of hypersensitivity to rHA.

Pregnancy
The vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see sections 4.3 and 4.6).

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-RVAXPRO (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
Individuals who are known to be infected with human immunodeficiency viruses and are *not* immunocompromised may be vaccinated. However, these vaccinees should be monitored closely for measles, mumps, and rubella because vaccination may be less effective in these patients than in persons not infected with human immunodeficiency viruses (see section 4.3).

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 on the effect of measles virus vaccines on children with untreated tuberculosis (see section 4.3).

As for any vaccine, vaccination with M-M-RVAXPRO 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Administration of immune globulins concomitantly with M-M-RVAXPRO 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-RVAXPRO unless considered to be essential.

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-RVAXPRO.

Use with other vaccines
Currently no specific studies have been conducted on the concomitant use of M-M-RVAXPRO and other vaccines. However, since M-M-RVAXPRO 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-RVAXPRO 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-RVAXPRO 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
Studies have not been conducted with M-M-RVAXPRO in pregnant women. It is not known whether M-M-RVAXPRO can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see sections 4.3 and 4.4).

In order to advise 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) In a 10 year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome; (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 foetus, there is no evidence that it causes congenital malformations in humans; and (3) Reports have indicated that contracting wild-type measles during pregnancy enhances foetal 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 foetal effects.

Note: Official recommendations may vary regarding the duration of the waiting period that is recommended for avoiding pregnancy following vaccination.

Postpartum Women
It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period.

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-RVAXPRO is administered to a breast-feeding woman.

Fertility
Animal reproduction studies have not been conducted with M-M-RVAXPRO. M-M-RVAXPRO has not been evaluated for potential to impair fertility.

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.

4.8 Undesirable effects

In clinical trials, M-M-RVAXPRO 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-RVAXPRO, 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 following vaccine-related adverse reactions were observed in individuals following vaccination with M-M-RVAXPRO (excluding isolated reports with frequency <0.2%).

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

Additionally, other adverse experiences reported with post-marketing use of M-M-RVAXPRO 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 below (frequency *not known*). These data were reported based on more than 400 million doses distributed worldwide.

[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)]

Infections and infestations
Uncommon: nasopharyngitis, upper respiratory tract infection or viral infection
Not known: aseptic meningitis (see below), atypical measles, epididymitis, orchitis, otitis media, parotitis, rhinitis, subacute sclerosing panencephalitis (see below)

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.

Blood and the lymphatic system disorders
Not known: regional lymphadenopathy, thrombocytopenia

Immune system disorders
Not known: anaphylactoid reaction, anaphylaxis and related phenomenon such as angioneurotic oedema, facial oedema, and peripheral oedema

Psychiatric disorders
Not known: irritability

Nervous system disorders
Not known: afebrile convulsions or seizures, ataxia, dizziness, encephalitis (see below), encephalopathy (see below), 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

Encephalitis and encephalopathy, excluding subacute sclerosing panencephalitis (SSPE), have been reported approximately once for every 3 million doses of the measles-containing vaccines manufactured by Merck & Co., Inc. Post-marketing surveillance of the more than 400 million doses that have been distributed worldwide over nearly 25 years (1978-2003) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. In no case has it been shown conclusively that reactions were actually caused by vaccine; however, the data suggest the possibility that some of these cases may have been caused by measles vaccines.

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.

Eye disorders
Not known: conjunctivitis, retinitis

Ear and labyrinth disorders
Not known: nerve deafness

Respiratory, thoracic, and mediastinal disorders
Uncommon: rhinorrhoea
Not known: bronchial spasm, cough, pneumonia, pneumonitis (see section 4.3), sore throat

Gastrointestinal disorders
Uncommon: diarrhoea or vomiting
Not known: nausea

Skin and subcutaneous tissue disorders
Common: rash morbilliform or other rash
Uncommon: urticaria
Not known: panniculitis, purpura, skin induration, Stevens-Johnson syndrome, pruritus

Musculoskeletal, connective tissue and bone disorders
Not known: arthritis and/or arthralgia (usually transient and rarely chronic [see below]), myalgia

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 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.
General disorders and administration site conditions
Very common: fever (38.5°C or higher), injection site erythema, injection site pain, and injection site swelling
Common: injection site bruising
Uncommon: injection site rash
Not known: burning and/or stinging of short duration at the injection site, fever (38.5°C or higher), malaise, papillitis, peripheral oedema, swelling, tenderness, vesicles at the injection site, wheal and flare at the injection site

Vascular disorders
Not known: vasculitis

4.9 Overdose

Overdose has been reported rarely and was not associated with any serious adverse reactions.

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

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Traditional non-clinical studies were not performed, but there are no non-clinical concerns considered relevant to clinical safety beyond data included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sorbitol
Sodium phosphate
Potassium phosphate
Sucrose
Hydrolysed gelatin
Medium 199 with Hanks' salts
Minimum Essential Medium, Eagle (MEM)
Monosodium L-glutamate
Neomycin
Phenol red
Sodium bicarbonate
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

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. Protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Powder in a vial (Type 1 glass) with a stopper (butyl rubber) and solvent in a vial (Type 1 glass) with stopper (chlorobutyl rubber) in a pack size of 1 and 10.

Not all pack sizes may be marketed.

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. 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.

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.

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

7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/337/001
EU/1/06/337/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/05/2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

M-M-RVAXPRO
Powder and solvent for suspension for injection in pre-filled syringe.
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.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection in pre-filled syringe.

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-RVAXPRO is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months or older (see section 4.2).

M-M-RVAXPRO 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.

4.2 Posology and method of administration

Posology

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

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-RVAXPRO 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. 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-RVAXPRO for use in children below9 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.

Precautions to be taken before handling or administering the medicinal product
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 (see also sections 4.4 and 4.6).

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

Active untreated tuberculosis (see section 4.4).

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-RVAXPRO is not contraindicated in individuals who are receiving topical or low-dose parenteral corticosteroids (***e.g.*** for asthma prophylaxis or replacement therapy).

Humoral or cellular (primary or acquired) immunodeficiency, including hypogammaglobulinemia and dysgammaglobulinemia and AIDS, or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage <25% (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

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

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-RVAXPRO 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).

The vaccine contains 1.9 mg of sucrose as an excipient. This amount is too low to cause adverse events in patients with rare hereditary problems such as fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.

The vaccine contains residual traces of recombinant human albumin (rHA). In a study with children receiving a second dose of M-M-RVAXPRO, sensitisation to rHA was not observed. A theoretical risk of hypersensitivity to rHA at a low frequency cannot be ruled out. Therefore caution needs to be exercised when using any product containing rHA in individuals who previously showed signs of hypersensitivity to rHA.

Pregnancy
The vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see sections 4.3 and 4.6).

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-RVAXPRO (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
Individuals who are known to be infected with human immunodeficiency viruses and are *not* immunocompromised may be vaccinated. However, these vaccinees should be monitored closely for measles, mumps, and rubella because vaccination may be less effective in these patients than in persons not infected with human immunodeficiency viruses (see section 4.3).

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 on the effect of measles virus vaccines on children with untreated tuberculosis (see section 4.3).

As for any vaccine, vaccination with M-M-RVAXPRO 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Administration of immune globulins concomitantly with M-M-RVAXPRO 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-RVAXPRO unless considered to be essential.

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-RVAXPRO.

Use with other vaccines

Currently no specific studies have been conducted on the concomitant use of M-M-RVAXPRO and other vaccines. However, since M-M-RVAXPRO 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-RVAXPRO 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-RVAXPRO 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
Studies have not been conducted with M-M-RVAXPRO in pregnant women. It is not known whether M-M-RVAXPRO can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see sections 4.3 and 4.4).

In order to advise 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) In a 10 year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome; (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 foetus, there is no evidence that it causes congenital malformations in humans; and (3) Reports have indicated that contracting wild-type measles during pregnancy enhances foetal 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 foetal effects.

Note: Official recommendations may vary regarding the duration of the waiting period that is recommended for avoiding pregnancy following vaccination.

Postpartum Women
It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period.

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-RVAXPRO is administered to a breast-feeding woman.

Fertility
Animal reproduction studies have not been conducted with M-M-RVAXPRO. M-M-RVAXPRO has not been evaluated for potential to impair fertility.

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.

4.8 Undesirable effects

In clinical trials, M-M-RVAXPRO 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-RVAXPRO, 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 following vaccine-related adverse reactions were observed in individuals following vaccination with M-M-RVAXPRO (excluding isolated reports with frequency <0.2%).

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

Additionally, other adverse experiences reported with post-marketing use of M-M-RVAXPRO 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 below (frequency *not known*). These data were reported based on more than 400 million doses distributed worldwide.

[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)]

Infections and infestations
Uncommon: nasopharyngitis, upper respiratory tract infection or viral infection
Not known: aseptic meningitis (see below), atypical measles, epididymitis, orchitis, otitis media, parotitis, rhinitis, subacute sclerosing panencephalitis (see below)

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.

Blood and the lymphatic system disorders
Not known: regional lymphadenopathy, thrombocytopenia

Immune system disorders
Not known: anaphylactoid reaction, anaphylaxis and related phenomenon such as angioneurotic oedema, facial oedema, and peripheral oedema

Psychiatric disorders
Not known: irritability

Nervous system disorders
Not known: afebrile convulsions or seizures, ataxia, dizziness, encephalitis (see below), encephalopathy (see below), 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

Encephalitis and encephalopathy, excluding subacute sclerosing panencephalitis (SSPE), have been reported approximately once for every 3 million doses of the measles-containing vaccines manufactured by Merck & Co., Inc. Post-marketing surveillance of the more than 400 million doses that have been distributed worldwide over nearly 25 years (1978-2003) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. In no case has it been shown conclusively that reactions were actually caused by vaccine; however, the data suggest the possibility that some of these cases may have been caused by measles vaccines.

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.

Eye disorders
Not known: conjunctivitis, retinitis

Ear and labyrinth disorders
Not known: nerve deafness

Respiratory, thoracic, and mediastinal disorders
Uncommon: rhinorrhoea
Not known: bronchial spasm, cough, pneumonia, pneumonitis (see section 4.3), sore throat
Gastrointestinal disorders
Uncommon: diarrhoea or vomiting

Not known: nausea

Skin and subcutaneous tissue disorders
Common: rash morbilliform or other rash
Uncommon: urticaria
Not known: panniculitis, purpura, skin induration, Stevens-Johnson syndrome, pruritus

Musculoskeletal, connective tissue and bone disorders
Not known: arthritis and/or arthralgia (usually transient and rarely chronic [see below]), myalgia

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 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.

General disorders and administration site conditions
Very common: fever (38.5°C or higher), injection site erythema, injection site pain, and injection site swelling
Common: injection site bruising
Uncommon: injection site rash
Not known: burning and/or stinging of short duration at the injection site, fever (38.5°C or higher), malaise, papillitis, peripheral oedema, swelling, tenderness, vesicles at the injection site, wheal and flare at the injection site

Vascular disorders
Not known: vasculitis

4.9 Overdose

Overdose has been reported rarely and was not associated with any serious adverse reactions.

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

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Traditional non-clinical studies were not performed, but there are no non-clinical concerns considered relevant to clinical safety beyond data included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sorbitol
Sodium phosphate
Potassium phosphate
Sucrose
Hydrolysed gelatin
Medium 199 with Hanks' salts
Minimum Essential Medium, Eagle (MEM)
Monosodium L-glutamate
Neomycin
Phenol red
Sodium bicarbonate
Hydrochloric acid (to adjust pH)
Sodium hydroxide (to adjust pH)

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. Protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Powder in a vial (Type 1 glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe (Type 1 glass) with attached needle with plunger stopper (chlorobutyl rubber) and needle-shield (natural rubber) in a pack size of 1 and 10.

Powder in a vial (Type 1 glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe (Type 1 glass) with plunger stopper and tip cap (chlorobutyl rubber), without needle, in pack size 1, 10, and 20.

Powder in a vial (Type 1 glass) with a stopper (butyl rubber) and solvent in a pre-filled syringe (Type 1 glass) with plunger stopper and tip cap (chlorobutyl rubber), with one or two unattached needles, in pack size 1, 10 and 20.

Not all pack sizes may be marketed.

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

Inject the entire content of the syringe into the vial containing the powder. Gently agitate to mix thoroughly. 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.

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.

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

7. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/337/003
EU/1/06/337/004
EU/1/06/337/005
EU/1/06/337/006
EU/1/06/337/007
EU/1/06/337/008
EU/1/06/337/009
EU/1/06/337/010
EU/1/06/337/011
EU/1/06/337/012
EU/1/06/337/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/05/2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE ANDMANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Merck Sharp & Dohme Corp.
Sumneytown Pike
PO Box 4
West Point
Pennsylvania 19486
USA

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.1 of the Risk Management Plan (RMP) presented in Module 1.8.2.of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached

- At the request of the European Medicines Agency.

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

M-M-RVAXPRO - Powder in vial and solvent in vial- Pack of 1, 10

1. NAME OF THE MEDICINAL PRODUCT

M-M-RVAXPRO
Powder and solvent for suspension for injection
Measles, mumps, and rubella vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains:

Measles virus Enders' Edmonston strain (live attenuated)	not less than 1 $x10^3$ CCID50*
Mumps virus Jeryl Lynn™ [Level B] strain (live attenuated)	not less than 12,5 $x10^3$ CCID50*
Rubella virus Wistar RA 27/3 strain (live attenuated)	not less than 1 $x10^3$ CCID50*

* 50% cell culture infectious dose

3. LIST OF EXCIPIENTS

Sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolysed gelatine, medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid , sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection
One single dose vial (powder) and one single dose vial (solvent).
10 single dose vials (powder) and 10 single dose vials (solvent).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) or subcutaneous (SC) use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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
After reconstitution, use immediately or within 8 hours if stored in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Please read the package leaflet for disposal of medicines no longer required

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/337/001 – pack of 1
EU/1/06/337/002 – pack of 10

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS IN USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

M-M-RVAXPRO
Powder for suspension for injection.

2. METHOD OF ADMINISTRATION

IM or SC use

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for **M-M-RVAXPRO**
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

M-M-RVAXPRO - Powder in vial and solvent in prefilled syringe with attached needle - Pack of 1, 10

1. NAME OF THE MEDICINAL PRODUCT

M-M-RVAXPRO
Powder and solvent for suspension for injection in pre-filled syringe
Measles, mumps, and rubella vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains:

Measles virus Enders' Edmonston strain (live attenuated)	not less than $1x10^3$ CCID50*
Mumps virus Jeryl Lynn™ [Level B] strain (live attenuated)	not less than $12,5\ x10^3$ CCID50*
Rubella virus Wistar RA 27/3 strain (live attenuated)	not less than $1\ x10^3$ CCID50*

*50% cell culture infectious dose

3. LIST OF EXCIPIENTS

Sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolysed gelatin medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid , sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in pre-filled syringe
One single dose vial (powder) and one single dose prefilled syringe with attached needle (solvent).
10 single dose vials (powder) and 10 single dose prefilled syringes with attached needle (solvent).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) or subcutaneous (SC) use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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
After reconstitution, use immediately or within 8 hours if stored in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Please read the package leaflet for disposal of medicines no longer required

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/337/003 – pack of 1
EU/1/06/337/004 – pack of 10

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

M-M-RVAXPRO - Powder in vial and solvent in prefilled syringe without needle - Pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

M-M-RVAXPRO
Powder and solvent for suspension for injection in pre-filled syringe
Measles, mumps, and rubella vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains:

Measles virus Enders' Edmonston strain (live attenuated)	not less than 1 $x10^3$ CCID50*
Mumps virus Jeryl Lynn™ [Level B] strain (live attenuated)	not less than 12,5 $x10^3$ CCID50*
Rubella virus Wistar RA 27/3 strain (live attenuated)	not less than 1 $x10^3$ CCID50*

*50% cell culture infectious dose

3. LIST OF EXCIPIENTS

Sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolysed gelatine, medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid , sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in pre-filled syringe
One single dose vial (powder) and one single dose prefilled syringe without needle (solvent).
10 single dose vials (powder) and 10 single dose prefilled syringes without needle (solvent).
20 single dose vials (powder) and 20 single dose prefilled syringes without needle (solvent).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) or subcutaneous (SC) use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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
After reconstitution, use immediately or within 8 hours if stored in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Please read the package leaflet for disposal of medicines no longer required

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/337/005 – pack of 1
EU/1/06/337/006 – pack of 10
EU/1/06/337/007 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

M-M-RVAXPRO - Powder in vial and solvent in pre-filled syringe with one unattached needle – Pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

M-M-RVAXPRO
Powder and solvent for suspension for injection in pre-filled syringe
Measles, mumps, and rubella vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains:

Measles virus Enders' Edmonston strain (live attenuated)	not less than 1 $x10^3$ CCID50*
Mumps virus Jeryl Lynn™ [Level B] strain (live attenuated)	not less than 12,5 $x10^3$ CCID50*
Rubella virus Wistar RA 27/3 strain (live attenuated)	not less than 1 $x10^3$ CCID50*

*50% cell culture infectious dose

3. LIST OF EXCIPIENTS

Sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolysed gelatine, medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid , sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in pre-filled syringe
One single dose vial (powder) and one single dose prefilled syringe with one unattached needle (solvent).
10 single dose vials (powder) and 10 single dose prefilled syringes with one unattached needle (solvent).
20 single dose vials (powder) and 20 single dose prefilled syringes with one unattached needle (solvent).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) or subcutaneous (SC) use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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
After reconstitution, use immediately or within 8 hours if stored in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Please read the package leaflet for disposal of medicines no longer required

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/337/008 – pack of 1
EU/1/06/337/009 – pack of 10
EU/1/06/337/010 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

M-M-RVAXPRO - Powder in vial and solvent in pre-filled syringe with two unattached needles - Pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

M-M-RVAXPRO
Powder and solvent for suspension for injection in pre-filled syringe
Measles, mumps, and rubella vaccine (live)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one dose (0.5 ml) contains:

Measles virus Enders' Edmonston strain (live attenuated)	not less than 1 $x10^3$ CCID50*
Mumps virus Jeryl Lynn™ [Level B] strain (live attenuated)	not less than 12,5 $x10^3$ CCID50*
Rubella virus Wistar RA 27/3 strain (live attenuated)	not less than 1 $x10^3$ CCID50*

*50% cell culture infectious dose

3. LIST OF EXCIPIENTS

Sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolysed gelatine, medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid , sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection in pre-filled syringe
One single dose vial (powder) and one single dose prefilled syringe with two unattached needles (solvent).
10 single dose vials (powder) and 10 single dose pre-filled syringes with two unattached needles (solvent).
20 single dose vials (powder) and 20 single dose pre-filled syringes with two unattached needles (solvent).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) or subcutaneous (SC) use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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
After reconstitution, use immediately or within 8 hours if stored in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Please read the package leaflet for disposal of medicines no longer required

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR MSD SNC
8, rue Jonas Salk
F-69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/337/011 – pack of 1
EU/1/06/337/012 – pack of 10
EU/1/06/337/013 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

M-M-RVAXPRO
Powder for suspension for injection in pre-filled syringe

2. METHOD OF ADMINISTRATION

IM or SC use

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE OF SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for **M-M-RVAXPRO**
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

SANOFI PASTEUR MSD SNC

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

M-M-RVAXPRO
Powder and solvent for suspension for injection
Measles, mumps and rubella vaccine (live)

Read all of this leaflet before you or your child is vaccinated.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This vaccine has been prescribed for you or your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT M-M-RVAXPRO IS AND WHAT IT IS USED FOR

M-M-RVAXPRO is a vaccine containing measles, mumps, and rubella viruses that have been weakened. When a person is given the vaccine, the immune system (the body's natural defences) will make antibodies against the measles, mumps, and rubella viruses. The antibodies help protect against infections caused by these viruses.

M-M-RVAXPRO is given to help protect you or your child against measles, mumps, and rubella. The vaccine may be administered to persons 12 months of age or older.
M-M-RVAXPRO can be administered to infants from 9 to 12 months of age under special circumstances.

M-M-RVAXPRO can also be used in measles outbreaks, or for post-exposure vaccination, or for use in previously unvaccinated persons older than 9 months who are in contact with susceptible pregnant women, and persons likely to be susceptible to mumps and rubella.

Although M-M-RVAXPRO contains live viruses, they are too weak to cause measles, mumps, or rubella in healthy people.

2. BEFORE YOU USE M-M-RVAXPRO

Do not use M-M-RVAXPRO:
- If you or your child are allergic (hypersensitive) to any of the components of M-M-RVAXPRO (including neomycin or any of the ingredients listed under “other ingredients”. See section 6. Further information)
- If you or your child are pregnant (in addition, pregnancy should be avoided for 3 months after vaccination, see Pregnancy)
- If you or your child have active untreated tuberculosis
- If you or your child are receiving treatment or taking medicines that may weaken the immune system (except low-dose corticosteroid therapy for asthma or replacement therapy)
- If you or your child have a weakened immune system because of a disease (including AIDS)
- If you or your child have a blood disorder or any type of cancer that affects the immune system

- If you or your child have a family history of congenital or hereditary immunodeficiency, unless the immune competence of you or your child is demonstrated.
- If you or your child have any illness with fever higher than 38.5°C; however, low-grade fever itself is not a reason to delay vaccination

Take special care with M-M-RVAXPRO:
If the person to be vaccinated has experienced any of the following, talk to the doctor or pharmacist before M-M-RVAXPRO is given**:**
- If you or your child have an allergic reaction to eggs or anything that contained egg
- If you or your child have a history or family history of allergies or of convulsions (fits)
- If you or your child have a side effect after vaccination with measles, mumps, or rubella vaccine (in a single component vaccine or a combination vaccine, such as the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.) that involved easy bruising or bleeding for longer than usual
- If you or your child have infection with Human Immunodeficiency Virus (HIV) but do not show symptoms of HIV disease. You or your child should be monitored closely for measles, mumps, and rubella because vaccination may be less effective than for uninfected persons (see section **Do not use M-M-RVAXPRO**).

As with other vaccines, M-M-RVAXPRO may not completely protect all persons who are vaccinated. Also, if the person who is to be vaccinated has already been exposed to the measles, mumps, or rubella virus but is not yet ill, M-M-RVAXPRO may not be able to prevent the illness from appearing.

M-M-RVAXPRO can be given to persons who have been in recent (within 3 days) contact with a case of measles and may be incubating the disease. However, M-M-RVAXPRO may not always be able to prevent measles developing in these cases.

Using other medicines and other vaccines:

The doctor may delay your or your child's vaccination for at least 3 months following blood or plasma transfusions, or immune globulin (known as IG). After vaccination with M-M-RVAXPRO, IG should not be given for 1 month, unless your doctor tells you otherwise.

If a tuberculin test is to be performed, it should be done either any time before, simultaneously with, or 4 to 6 weeks after vaccination with M-M-RVAXPRO.

M-M-RVAXPRO may be given with Prevenar and/or hepatitis A vaccine at the same visit at a separate injection site (e.g. the other arm or leg).

M-M-RVAXPRO may be given with some routine childhood vaccines that may be due to be given at the same time. For vaccines that cannot be given at the same time, M-M-RVAXPRO should be given 1 month before or after administration of those vaccines.

Please tell your doctor or pharmacist if you or your child are taking or have recently taken any other medicines (or other vaccines), including medicines obtained without a prescription.

Pregnancy and breast-feeding
M-M-RVAXPRO must not be given to pregnant females. Females of child-bearing age should take the necessary precautions to avoid pregnancy for 3 months, or according to doctor's recommendation, after they have been given the vaccine.

Persons who are breast-feeding or intend to breast-feed should tell the doctor. The doctor will decide if M-M-RVAXPRO should be given.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

There is no information to suggest that M-M-RVAXPRO affects the ability to drive or operate machinery.

3. HOW TO USE M-M-RVAXPRO

M-M-RVAXPRO should be injected into the muscle or under the skin either in the area of the outer thigh or of the upper arm. Usually for injections into the muscle the thigh area is preferred in young children whereas for older individuals the upper arm area is the preferred injection site. M-M-RVAXPRO is not to be injected directly into any blood vessel.

M-M-RVAXPRO is given as follows:
One dose is given at an elected date usually from 12 months of age. Under special circumstances, it can be given from 9 months of age. Further doses should be administered according to your doctor's recommendation. The interval between 2 doses should be at least 4 weeks.

Reconstitution instructions intended for medical and healthcare professionals are included at the end of the leaflet

4. POSSIBLE SIDE EFFECTS

Like all medicines, M-M-RVAXPRO can cause side effects, although not everybody gets them.

Approximately 1 out of 10 patients reported the following side effects with the use of M-M-RVAXPRO: fever (38.5°C or higher), injection site redness, and injection site pain and swelling. Injection site bruising was reported in approximately 1 out of 100 patients.

Other side effects have been reported with the use of either the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. or of its monovalent (single) components: burning and/or stinging of short duration at the injection site, joint pain and/or swelling (which could be transient or chronic), rash, unusual bleeding or bruising under the skin, and swelling of the testicles.

Other less common side effects have been reported and some of these were serious. These included: allergic reactions, seizures (fits), and inflammation of the brain (encephalitis).

The doctor has a more complete list of side effects for M-M-RVAXPRO. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist. If the condition persists or worsens, seek medical attention.

5. HOW TO STORE M-M-RVAXPRO

Keep out of the reach and sight of children.
Store and transport refrigerated (2°C- 8°C).
Keep the vial of powder in the outer carton in order to protect from light.
Do not freeze the vaccine.
Do not use M-M-RVAXPRO after the expiry date which is stated on the outer carton after EXP.

Once the vaccine has been mixed with the solvent supplied, it should be either used immediately or stored in the refrigerator and used within eight hours.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What M-M-RVAXPRO contains

The active substances are:

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 other ingredients are:

***Powder*:**
sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolysed gelatin, medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid (to adjust pH), and sodium hydroxide (to adjust pH)

***Solvent*:**
water for injections

What M-M-RVAXPRO looks like and contents of the pack

The vaccine is a powder for suspension for injection contained in a single-dose vial, which should be mixed with solvent provided.

The solvent is a clear and colourless liquid. The powder is a light yellow compact crystalline cake.

M-M-RVAXPRO is available in packs of 1 and 10. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer Responsible for Batch Release: Merck Sharp and Dohme, B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien: Sanofi Pasteur MSD, Tél/Tel: +32.2.726.95.84
България: Мерк Шарп и Доум България ЕООД тел. + 359 2 8193740
Česká republika: Merck Sharp & Dohme, IDEA, Inc., org. sl., Tel.: +420.233.010.111
Danmark: Sanofi Pasteur MSD, +45 23 32 69 29
Deutschland: Sanofi Pasteur MSD GmbH, Tel: +49.6224.5940
Eesti: Merck Sharp & Dohme OÜ, Tel: +372.613.9750
Ελλάδα: ΒΙΑΝΕΞ Α.Ε., Τηλ: +30.210.8009111
España: Sanofi Pasteur MSD S.A., Tel: +34.91.371.78.00
France: Sanofi Pasteur MSD SNC, Tél: +33.4.37.28.40.00
Ireland: Sanofi Pasteur MSD Ltd, Tel: +3531.468.5600
Ísland: Sanofi Pasteur MSD, Sími: +32.2.726.95.84

Italia: Sanofi Pasteur MSD Spa, Tel: +39.06.664.092.11
Κύπρος: Merck Sharp & Dohme (Middle East) Limited., Τηλ: +357 22866700
Latvija: SIA Merck Sharp & Dohme Latvija, Tel: +371.67364.224
Lietuva: UAB Merck Sharp & Dohme, Tel.: +370.5.2780.247
Luxembourg/Luxemburg: Sanofi Pasteur MSD, Tél: +32.2.726.95.84
Magyarország: MSD Magyarország Kft, Tel.: + 36.1.888.5300
Malta: Merck Sharp & Dohme (Middle East) Limited, Tel: +357 22866700
Nederland: Sanofi Pasteur MSD, Tel: +31.23.567.96.00
Norge: Sanofi Pasteur MSD, Tlf: +47.67.50.50.20
Österreich: Sanofi Pasteur MSD GmbH, Tel: +43.1.866.70.22.202
Polska: MSD Polska Sp. z o.o., Tel.: +48.22.549.51.00
Portugal: Sanofi Pasteur MSD, SA, Tel: +351 21 470 45 50
România: Merck Sharp & Dohme Romania S.R.L. Tel: + 4021 529 29 00
Slovenija: Merck Sharp & Dohme, inovativna zdravila d.o.o. Tel: +386.1.520.4201
Slovenská republika: Merck Sharp & Dohme IDEA, Inc., Tel: +421.2.58282010
Suomi/Finland: Sanofi Pasteur MSD, Puh/Tel: +358.9.565.88.30
Sverige: Sanofi Pasteur MSD, Tel: +46.8.564.888.60
United Kingdom: Sanofi Pasteur MSD Ltd, Tel: +44.1.628.785.291

This leaflet was last approved in:

The following information is intended for medical or healthcare professionals only:

Reconstitution instructions
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.

Withdraw the entire volume of solvent into a syringe. 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 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.

It is recommended that the vaccine be administered immediately after reconstitution or stored in the refrigerator and used within 8 hours to minimize loss of potency. Discard if reconstituted vaccine is not used within 8 hours.

Do not freeze the reconstituted vaccine.

Do not use the reconstituted vaccine if you notice any particulate matter or if the appearance of the solvent or powder or of the reconstituted vaccine differs from that described above.

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

See also section 3 **HOW TO USE M-M-RVAXPRO**.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

M-M-RVAXPRO
Powder and solvent for suspension for injection in pre-filled syringe
Measles, mumps and rubella vaccine (live)

Read all of this leaflet before you or your child is vaccinated.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This vaccine has been prescribed for you or your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT M-M-RVAXPRO IS AND WHAT IT IS USED FOR

M-M-RVAXPRO is a vaccine containing measles, mumps, and rubella viruses that have been weakened. When a person is given the vaccine, the immune system (the body's natural defences) will make antibodies against the measles, mumps, and rubella viruses. The antibodies help protect against infections caused by these viruses.

M-M-RVAXPRO is given to help protect you or your child against measles, mumps, and rubella. The vaccine may be administered to persons 12 months of age or older.
M-M-RVAXPRO can be administered to infants from 9 to 12 months of age under special circumstances.

M-M-RVAXPRO can also be used in measles outbreaks, or for post-exposure vaccination, or for use in previously unvaccinated persons older than 9 months who are in contact with susceptible pregnant women, and persons likely to be susceptible to mumps and rubella.

Although M-M-RVAXPRO contains live viruses, they are too weak to cause measles, mumps, or rubella in healthy people.

2. BEFORE YOU USE M-M-RVAXPRO

Do not use M-M-RVAXPRO:
- If you or your child are allergic (hypersensitive) to any of the components of M-M-RVAXPRO (including neomycin or any of the ingredients listed under “other ingredients”. See section 6. Further information)
- If you or your child are pregnant (in addition, pregnancy should be avoided for 3 months after vaccination, see Pregnancy)
- If you or your child have active untreated tuberculosis
- If you or your child are receiving treatment or taking medicines that may weaken the immune system (except low-dose corticosteroid therapy for asthma or replacement therapy)
- If you or your child have a weakened immune system because of a disease (including AIDS)
- If you or your child have a blood disorder or any type of cancer that affects the immune system

- If you or your child have a family history of congenital or hereditary immunodeficiency, unless the immune competence of your or your child is demonstrated.
- If you or your child have any illness with fever higher than 38.5°C; however, low-grade fever itself is not a reason to delay vaccination

Take special care with M-M-RVAXPRO:
If the person to be vaccinated has experienced any of the following, talk to the doctor or pharmacist before M-M-RVAXPRO is given**:**
- If you or your child have an allergic reaction to eggs or anything that contained egg
- If you or your child have a history or family history of allergies or of convulsions (fits)
- If you or your child have a side effect after vaccination with measles, mumps, or rubella vaccine (in a single component vaccine or a combination vaccine, such as the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc.) that involved easy bruising or bleeding for longer than usual
- If you or your child have infection with Human Immunodeficiency Virus (HIV) but do not show symptoms of HIV disease. You or your child should be monitored closely for measles, mumps, and rubella because vaccination may be less effective than for uninfected persons (see section **Do not use M-M-RVAXPRO**).

As with other vaccines, M-M-RVAXPRO may not completely protect all persons who are vaccinated. Also, if the person who is to be vaccinated has already been exposed to the measles, mumps, or rubella virus but is not yet ill, M-M-RVAXPRO may not be able to prevent the illness from appearing.

M-M-RVAXPRO can be given to persons who have been in recent (within 3 days) contact with a case of measles and may be incubating the disease. However, M-M-RVAXPRO may not always be able to prevent measles developing in these cases.

Using other medicines and other vaccines:

The doctor may delay your or your child's vaccination for at least 3 months following blood or plasma transfusions, or immune globulin (known as IG). After vaccination with M-M-RVAXPRO, IG should not be given for 1 month, unless your doctor tells you otherwise.

If a tuberculin test is to be performed, it should be done either any time before, simultaneously with, or 4 to 6 weeks after vaccination with M-M-RVAXPRO.

M-M-RVAXPRO may be given with Prevenar and/or hepatitis A vaccine at the same visit at a separate injection site (e.g. the other arm or leg).
M-M-RVAXPRO may be given with some routine childhood vaccines that may be due to be given at the same time. For vaccines that cannot be given at the same time, M-M-RVAXPRO should be given 1 month before or after administration of those vaccines.

Please tell your doctor or pharmacist if you or your child are taking or have recently taken any other medicines (or other vaccines), including medicines obtained without a prescription.

Pregnancy and breast-feeding
M-M-RVAXPRO must not be given to pregnant females. Females of child-bearing age should take the necessary precautions to avoid pregnancy for 3 months, or according to doctor's recommendation, after they have been given the vaccine.

Persons who are breast-feeding or intend to breast-feed should tell the doctor. The doctor will decide if M-M-RVAXPRO should be given.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

There is no information to suggest that M-M-RVAXPRO affects the ability to drive or operate machinery.

3. HOW TO USE M-M-RVAXPRO

M-M-RVAXPRO should be injected into the muscle under the skin either in the area of the outer thigh or of the upper arm. Usually for injections into the muscle the thigh area is preferred in young children whereas for older individuals the upper arm area is the preferred injection site. M-M-RVAXPRO is not to be injected directly into any blood vessel.

M-M-RVAXPRO is given as follows:
One dose is given at an elected date usually from 12 months of age. Under special circumstances, it can be given from 9 months of age. Further doses should be administered according to your doctor's recommendation. The interval between 2 doses should be at least 4 weeks.

Reconstitution instructions intended for medical and healthcare professionals are included at the end of the leaflet.

4. POSSIBLE SIDE EFFECTS

Like all medicines, M-M-RVAXPRO can cause side effects, although not everybody gets them.

Approximately 1 out of 10 patients reported the following side effects with the use of M-M-RVAXPRO: fever (38.5°C or higher), injection site redness, and injection site pain and swelling. Injection site bruising was reported in approximately 1 out of 100 patients.

Other side effects have been reported with the use of either the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. or of its monovalent (single) components: burning and/or stinging of short duration at the injection site, joint pain and/or swelling (which could be transient or chronic), rash, unusual bleeding or bruising under the skin, and swelling of the testicles.

Other less common side effects have been reported and some of these were serious. These included: allergic reactions, seizures (fits), and inflammation of the brain (encephalitis).

The doctor has a more complete list of side effects for M-M-RVAXPRO. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist. If the condition persists or worsens, seek medical attention.

5. HOW TO STORE M-M-RVAXPRO

Keep out of the reach and sight of children.
Store and transport refrigerated (2°C- 8°C).
Keep the vial of powder in the outer carton in order to protect from light.
Do not freeze the vaccine.
Do not use M-M-RVAXPRO after the expiry date which is stated on the outer carton after EXP.

Once the vaccine has been mixed with the solvent supplied, it should be either used immediately or stored in the refrigerator and used within eight hours.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What M-M-RVAXPRO contains

The active substances are:

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 other ingredients are:

***Powder*:**
sorbitol, sodium phosphate, potassium phosphate, sucrose, hydrolysed gelatin, medium 199 with Hanks' salts, MEM, monosodium L-glutamate, neomycin, phenol red, sodium bicarbonate, hydrochloric acid (to adjust pH), and sodium hydroxide (to adjust pH)

***Solvent*:**
water for injections

What M-M-RVAXPRO looks like and contents of the pack

The vaccine is a powder for suspension for injection contained in a single-dose vial, which should be mixed with solvent provided.

The solvent is a clear and colourless liquid. The powder is a light yellow compact crystalline cake.

M-M-RVAXPRO is available in packs of 1, 10 and 20, with or without needles. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer Responsible for Batch Release: Merck Sharp and Dohme, B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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United Kingdom: Sanofi Pasteur MSD Ltd, Tel: +44.1.628.785.291

This leaflet was last approved in:

The following information is intended for medical or healthcare professionals only:

Reconstitution instructions
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.

Inject the entire content of the pre-filled syringe into the vial containing the powder. Gently agitate to dissolve completely. 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.

It is recommended that the vaccine be administered immediately after reconstitution or stored in the refrigerator and used within 8 hours to minimize loss of potency. Discard if reconstituted vaccine is not used within 8 hours.

Do not freeze the reconstituted vaccine.

Do not use the reconstituted vaccine if you notice any particulate matter or if the appearance of the solvent or powder or of the reconstituted vaccine differs from that described above.

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

See also section 3 **HOW TO USE M-M-RVAXPRO**.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.