IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0544/024/001
Case No: 2052579

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Sanofi Pasteur MSD Ltd

Block A, Second Floor, **Cookstown Court, Old Belgard Road**, **Tallaght**, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

M-M-RTM II

Powder and Solvent for Solution for Injecton in a pre-filled syringe

Measles, Mumps and Rubella Vaccine, Live, Attenuated

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **06/08/2008** until **07/05/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

M-M-R ^{TM} II
Powder and Solvent for Solution for Injection in a pre-filled syringe
Measles, Mumps and Rubella Vaccine, Live, Attenuated

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 millilitre dose when reconstituted contains not less than equivalent of:

1,000 $TCID_{50}$* of measles Virus Live.
(the more attenuated Enders Line of the Edmonston strain).

20,000 $TCID_{50}$ of Mumps Virus Live (Jeryl Lynn Level B strain).

1,000 $TCID_{50}$ of Rubella Virus Live (Wistar, RA 27/3 Strain).

*Tissue Culture Infectious Dose.

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection in a prefilled syringe

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For simultaneous vaccination against measles, mumps and rubella in the following groups:

Children: Recommended for both primary and booster immunisation of both boys and girls 12 months of age or older.

Non-Pregnant Adolescent and Adult Females: Immunisation of susceptible non-pregnant adolescent and adult females of childbearing age is indicated when the potential vaccinee agrees not to become pregnant for the next 3 months after vaccination and is informed of the reason, (this also applies to women in the immediate post-partum period when it may be found most convenient to vaccinate, see also 4.6 Pregnancy and Lactation), and is told of the frequent occurrence of generally self-limiting arthralgia and/or arthritis beginning 2-4 weeks after vaccination.

International Travellers: Individuals planning travel abroad who are known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps or rubella), if available, or a combined antigen vaccine as appropriate. A combined measles, mumps and rubella vaccine is preferred for persons likely to be susceptible to mumps and rubella as well as measles.

4.2 Posology and method of administration

The vaccine is administered by deep subcutaneous or intramuscular injection preferably into the outer aspect of the arm.

Children who suffered Idiopathic Thrombocytopenic Purpura (ITP) within six weeks of the first dose of MMR (or its component vaccines), should have serological status evaluated at the time the second dose was due. If serology testing suggests that a child is not fully immune against measles, mumps and rubella then a second dose of MMR is recommended (see 4.4).

Adults and children: After suitably cleansing the injection site, 0.5 millilitre of reconstituted vaccine should be injected. M-M-R™ II must not be given intravenously.

Do not give immunoglobulin with M-M-R™ II.

Warning: A sterile syringe and epinephrine (adrenaline) injection should be available for immediate use should an anaphylactic reaction occur.

Elderly: No special comment.

Revaccination: A second dose of measles, mumps and rubella vaccine is recommended in the national immunisation schedule (see 4.4).

Children receiving their first dose of measles, mumps and rubella vaccine younger than 12 months of age should be revaccinated at 15 months of age. They may still receive a further dose at the time indicated in the national immunisation schedule, (M-M-R™ II is not recommended for infants under 12 months of age).

Use with other vaccines: Vaccines containing diphtheria, tetanus and pertussis antigens and/or oral poliomyelitis vaccine can be administered at the same time as M-M-R™ II. For concurrent parenteral vaccination, separate syringes and separate sites for injection should be used. M-M-R™ II should not be given less than one month before or after immunisation with other live viral vaccines.

4.3 Contraindications

Do not give M-M-R™ II to pregnant females; the possible effects of the vaccine on foetal development are unknown at this time. Pregnancy must be avoided for three months following vaccination of post-pubertal females.

Anaphylactic or anaphylactoid reactions to a previous dose of vaccine or to neomycin or any other vaccine constituent. (Each dose of reconstituted vaccine contains approximately 25 micrograms neomycin.)

Any febrile respiratory illness, or other active or suspected infection.

Those with impaired immune responsiveness, whether occurring naturally or as a result of therapy with steroids, radiotherapy, cytotoxic or other agents. This contra-indication does not apply to patients receiving corticosteroids as replacement therapy, e.g. for Addisons's disease.

Patients with active untreated tuberculosis, blood dyscrasias such as thrombocytopenia, leukaemia, malignant disease including lymphomas of any type or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulnaemic and dysgammaglobulinaemic states.

Fatal cases of measles inclusion body encephalitis (MIBE) and pneumonitis as a direct consequence of disseminated measles vaccine virus infection have been reported in severely immunocompromised individuals vaccinated with measles-containing vaccine. Those patients with a family history of congenital hereditary immunodeficiency until their immune competence has been demonstrated.

Children below 12 months of age: Children below 12 months of age should not normally be given M-M-R™ II unless they are at special risk, since the presence of maternal antibody may interfere with their ability to respond. They may be given human normal immunoglobulin. However, where immunisation below the age of 12 months is deemed

necessary, a second dose of vaccine should be given at 15 months of age and a further dose may still be given at the usual time.

4.4 Special warnings and precautions for use

As with all vaccines, facilities for the management of anaphylaxis, including epinephrine (adrenaline), should always be available during vaccination.

Hypersensitivity to eggs: There is increasing evidence that M-M-R™ II can be given safely to children even if they have previously had an anaphylactic reaction (generalised urticaria, swelling of the mouth and throat, difficulty in breathing, hypotension or shock) following food containing egg. Nevertheless, caution should be observed and if there is concern, paediatric advice should be sought with a view to immunisation under controlled conditions such as admission to hospital as a day case.

M-M-R™ II should be given with caution to those with an individual or family history of cerebral injury or any other condition in which stress due to fever should be avoided. The physician should be alert to the rise in temperature that may follow vaccination.

Children and young adults, who are known to be infected with, or have a history of immunodeficiency viruses, but without overt clinical manifestations of immunosuppression, may be vaccinated; however, the vaccinees should be closely monitored for exposure to vaccine-preventable diseases because immunisation may be less effective than for uninfected persons. In selected cases, confirmation of circulating antibody levels may be indicated to help guide appropriate protective measures, including immunoprophylaxis if immunity has waned to non-protective levels.

Children who suffered idiopathic thrombocytopenia purpura (ITP) within 6 weeks of the first dose of MMR (or its component vaccines) should have serological status evaluated at the time the second dose was due. If serology testing suggests that a child is not fully immune against measles, mumps and rubella then a second dose of MMR is recommended.

Excretion of small amounts of live attenuated rubella virus from the nose and throat has occurred in the majority of susceptible individuals 7-28 days after vaccination. There is no definite evidence to indicate that such a virus is transmitted to susceptible persons who are in contact with vaccinated individuals.

Consequently, transmission, while accepted as a theoretical possibility, has not been regarded as a significant risk. However, transmission of the vaccine virus via breast milk has been documented.

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

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

Parents of children with a personal or family history of convulsions or idiopathic epilepsy should be advised that such children have a small increased risk of seizures following vaccination and be informed in advance of procedures for their management.

As for any vaccine, vaccination with M-M-R™ II may not result in protection in 100% of vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccination should be deferred for at least three months following blood or plasma transfusions or administration of any human immune serum globulin. If any of these substances has been used near to the time of vaccination with M-M-R™II, a test should subsequently be performed to confirm successful seroconversions.

Where anti-Rho (D) globulin (human) and rubella vaccine are required in the immediate post-partum period, rubella

vaccine alone and not M-M-R™II should be used.
It has been reported that live attenuated measles, mumps and rubella vaccine may temporarily depress tuberculin skin sensitivity. If a tuberculin test is to be done, it should be administered before or simultaneously with M-M-R™II.

4.6 Pregnancy and lactation

Pregnant females: Pregnant females must NOT be given M-M-R™ II. Furthermore, pregnancy should be avoided for three months following vaccination (see 'Contra-indications').

Animal reproduction studies have not been conducted with M-M-R™ II. It is also not known whether M-M-R™ II can cause foetal harm when given to pregnant women or affect reproductive capacity.

If a woman is inadvertently vaccinated or if she becomes pregnant within three months of vaccination, she should be counselled by her physician.

It has been established that:

1) in a ten-year study involving 700 pregnant women who received rubella vaccination within three months of conception, none of their new-born infants had abnormalities compatible with a congenital rubella syndrome;

2) although mumps virus is capable of infecting the placenta and foetus, there is no good evidence that it causes congenital malformations in humans.

Mumps vaccine virus has also been shown to affect the placenta, but the virus has not been isolated from foetal tissues taken from susceptible women who were vaccinated and underwent elective abortions; and

3) reports indicate that contracting natural measles during pregnancy increases the rates of spontaneous abortion, stillbirth, congenital defects and prematurity. Although there are no adequate studies on the attenuated (vaccine) strain in pregnancy, it would be prudent to assume that the strain of the virus in the vaccine is also capable of inducing adverse foetal effects.

Breast-feeding mothers: Caution should be exercised when M-M-R™ II is given to a breast-feeding mother. Although it is not known whether measles or mumps vaccine virus is secreted in human milk, studies have shown that breast-feeding mothers immunised with live attenuated RA 27/3 strain rubella vaccine transmit the virus via breast milk. In those babies with serological evidence of rubella, none showed clinical disease.

4.7 Effects on ability to drive and use machines

The use of M-M-R™ II generally does not interfere with the ability to drive or operate machinery.

4.8 Undesirable effects

Adverse reactions: Adverse reactions associated with M-M-R™ II are similar to those to be expected from the administration of monovalent vaccines given separately.

The following adverse reactions occur commonly:

- Burning and/or stinging at the injection site for a short period.

The following adverse reactions occur occasionally:

- Body as a whole: Fever (+38.3^{o}C (+101^{o}F) or higher).
- Skin: Rash, usually minimal but may be generalised.
- Generally, fever, rash or both, appear between the 5th and the 12th days.
- Mild, local reactions such as erythema; induration and tenderness.

The following adverse reactions occur rarely:

- Body as a whole: Sore throat, malaise, atypical measles, syncope, irritability.
- Digestive: Parotitis, nausea, vomiting, diarrhoea.
- Haematologic/lymphatic: Regional lymphadenopathy, thrombocytopenia, purpura.
- Hypersensitivity: Allergic reactions such as wheal and flare at injection site, anaphylaxis and anaphylactoid reactions, as well as related phenomena such as angioneurotic oedema (including peripheral or facial oedema) and bronchial spasm, urticaria in individuals with or without an allergic history.
- Musculoskeletal: Arthralgia and/or arthritis (usually transient and rarely chronic), myalgia.
- Nervous/Psychiatric: Febrile convulsions in children, afebrile convulsion or seizures, headache, dizziness, paraesthesia, polyneuritis, polyneuropathy, Guillain-Barré syndrome, ataxia, measles inclusion body encephalitis (MIBE) (see 4.3).
- Encephalitis/encephalopathy have been reported approximately once for every 3 million doses. In no cases has it been shown that reactions were actually caused by vaccine. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (1 per 2000 reported cases).
- Respiratory System: Pneumonitis (see 4.3), cough, rhinitis, pneumonia.
- Skin: Erythema multiforme, Stevens-Johnson syndrome, vesiculation at injection site, swelling.
- Special senses: Forms of optic neuritis, including retrobulbar neuritis, papillitis, and retinitis; ocular palsies, otitis media, nerve deafness, conjunctivitis.
- Urogenital: Orchitis, epididymitis.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognised measles in the first year of life or possibly from the measles vaccination. Based on the estimated nationwide measles vaccine distribution in the USA, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less that the association with natural measles: 6-22 cases of SSPE per million cases of measles.

A study suggests that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

Local reactions characterised by marked swelling, redness and vesiculation at the injection site of attenuated live measles virus vaccines and systemic reactions including atypical measles have occurred in vaccinees who had previously received killed measles vaccine. Rarely, there have been reports of more severe reactions, including prolonged high fevers and extensive local reactions requiring hospitalisation.

Panniculitis has also been reported rarely following vaccination with measles vaccine.

Arthralgia or arthritis, or both, are usually transient and rarely chronic features of natural rubella. Like polyneuritis that is also a feature of natural infection, their frequency and severity vary with age and sex, being greatest in adult females and least in prepubertal children.

The chronic arthritis associated with natural rubella has been related to virus and/or viral antigen found in body tissues. Only rarely have vaccinees developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0-3%; women: 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 in adult women. Even in older women (35-45 years) these reactions are generally well tolerated and rarely interfere with normal activities.

4.9 Overdose

Poisoning is unlikely. Swallowing M-M-R™ II would render the live attenuated vaccine benign, and the content of the neomycin (25 mocrograms/0.5 millilitre) is not likely to cause toxicity.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

M-M-R™II vaccine is a mixture of live attenuated measles, mumps and rubella viruses to provide active immunisation against these diseases.

Clinical studies in 279 triple seronegative children aged 11 months to 7 years, showed that M-M-R™II is highly immunogenic and generally well-tolerated.
In these studies, a single injection of the vaccine induced measles haemagglutination-inhibition (HI) antibodies in 95%, mumps neutralising antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons.
Based on available evidence a second dose of measles, mumps and rubella vaccine in the national immunisation schedule has the potential to prevent epidemics of measles and overall is as well-tolerated as primary immunisation.

Vaccine induced antibody levels following administration of M-M-R™II have been shown to persist for over 11 years.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No further information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vaccine:
Human albumin solution (which contains sodium caprylate, sodium
N-acetyltryptophanate, sodium hydrogen carbonate, glacial acetic acid, and sodium hydroxide)
Sodium phosphate, monobasic
Sodium phosphate, dibasic
Sodium hydrogen carbonate
Medium 199[1]
Minimum essential medium, eagle[2]
Neomycin sulphate
Phenol red
Sorbitol
Potassium phosphate, monobasic
Potassium phosphate, dibasic
Gelatin (porcine) hydrolysed
Sucrose
Monosodium L-glutamate

[1]Medium199 is a complex mixture of amino acids (including phenylalanine), mineral salts, vitamins and other components (including glucose).

[2]Minimum essential medium, eagle is a mixture of amino acids, mineral salts and vitamins.

Solvent:
Sterile water

6.2 Incompatibilities

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

6.3 Shelf Life

Shelf life of the medicinal product as packaged for sale: 18 months.

Shelf life after reconstitution: Use immediately.

6.4 Special precautions for storage

Store between +2°C and +8°C. Protect from light, do not freeze. The reconstituted vaccine should be used immediately.

6.5 Nature and contents of container

Powder for solution for injection
3 ml (Type I, Ph. Eur.) glass tubing vials with 13 ml (West Co grey butyl 1816) lyophilisation stoppers and 13 millimetres 1 piece flip-off aluminium seal with plastic cap.

Solvent for parenteral use
1 millilitre type 1 borosillicate glass pre-filled syringe with chlorobuty 1 rubber stopper and tip cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

To reconstitute the vaccine, all the solvent provided should be injected into a vial of lyophilised vaccine, and this agitated to ensure thorough mixing. All the reconstituted vaccine is then drawn into the syringe and injected subcutaneously or intramuscularly.

Only the solvent supplied should be used for reconstitution, since it is free of preservatives and other antiviral substances that may inactivate the vaccine.

A separate sterile disposable needle and syringe should be used for each vaccinee.

It is good practice to record title, dose and batch number of all vaccines and dates of administration.

When reconstituted, the vaccine is yellow. It is acceptable for use only when clear and free from particulate matter.

The vaccine should be used immediately after reconstitution. Protect from light at all times, since exposure may inactivate the virus.

7 MARKETING AUTHORISATION HOLDER

Sanofi Pasteur MSD
Block A, Second Floor
Cookstown Court
Old Belgard Road,
Tallaght,
Dublin 24.

8 MARKETING AUTHORISATION NUMBER

PA 544/24/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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